The Development of Health Costs in Oncology – The Role of Predictive Markers in Breast and Colorectal Cancer

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DISSERTATION

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“There is always a way to do it better… find it!”

Thomas A Edison (Feb 11, 1847–Oct 18, 1931)

Dedication

Meinen geliebten Eltern sowie meiner Schwester für die stetige Unterstützung und Liebe.

Preface

Is it appropriate to treat newly diagnosed cancer patients with all existing therapies to achieve a survival benefit? Side effects, toxicities and also high costs restrain such an approach. To enhance the efficiency of cancer therapies, it is of highest importance to apply accurate, validated and powerful markers predictive of treatment response. The aim of this work was to assess the cost-effectiveness of predictive markers in breast and colorectal cancer settings. The fundamentals of pharmacoeconomic evaluations, the burden of breast and colorectal cancer and the role of predictive markers in oncology are first introduced. The core data is then presented in form of the following three publications or submitted manuscripts for publication:

1. **Human epidermal growth factor receptor 2 expression in early breast cancer patients: a Swiss cost–effectiveness analysis of different predictive assay strategies**
   Blank PR, Schwenkglenks M, Moch H, Szucs TD
   Breast Cancer Res Treat. 2010 Apr 3.
   Impact factor: 4.696

2. **Cost Effectiveness of Cytotoxic and Targeted Therapy for Metastatic Breast Cancer: A Critical and Systematic Review**
   Blank PR, Dedes KJ, Szucs TD
   Pharmacoeconomics. 2010 Aug 1;28(8):629-47
   Impact factor: 2.612

3. **Predictive testing for KRAS and BRAF mutations in the treatment of metastatic colorectal cancer – A cost-effectiveness analysis from the Swiss perspective**
   Blank PR, Moch H, Szucs TD, Schwenkglenks M
   Submitted manuscript

The work of this thesis was performed in the working group of Health Economics at the Institute of Social and Preventive Medicine at the University of Zurich in collaboration with the Institute of Surgical Pathology at the Department of Pathology at the University Hospital Zurich. The work was funded by an unrestricted educational grant of the ETH Foundation and the Competence Center for Systems Physiology and Metabolic Diseases (CC-SPMD), Zurich, Switzerland.

Contents

Part I - Summary

Background. Despite extensive progress in surgery and chemotherapy treatments, patients with advanced cancer in particular generally have a poor prognosis. Monoclonal antibody therapies against molecular markers like the epidermal growth factor receptor (EGFR) or the human epidermal growth factor receptor 2 (HER-2) have achieved substantial benefits in colorectal and breast cancer patients, but also increased health care costs. However, only those breast cancer patients with HER-2 protein overexpression or HER-2 oncogene amplification profit from trastuzumab, a monoclonal antibody targeted at HER-2. Recent clinical evidence has linked KRAS and BRAF mutations with resistance to EGFR antibodies like cetuximab. HER-2 status can be determined by immunohistochemistry (IHC) and/or fluorescence in situ hybridisation (FISH), whereas KRAS and BRAF mutations are generally identified by DNA sequencing analyses. It is a clinical and economic need to identify those patients who benefit from the expensive anti-cancer drugs. Data on the health economic consequence of predictive tests for HER-2, KRAS or BRAF are limited or even lacking.

Here, we assessed the cost-effectiveness of different test strategies for HER-2 in adjuvant breast cancer treatment. In addition, we determined the health economic impact of testing for KRAS and BRAF mutations in advanced, chemorefractory colorectal cancer patients from the perspective of the Swiss health system. Finally, pharmacoeconomic studies with regard to metastatic breast cancer were systematically and critically reviewed.

Methods. A life-long Markov state transition model was constructed to determine costs (€) and effectiveness (quality-adjusted life-years, QALYs) of predictive testing in hypothetical cohorts of early breast cancer and advanced chemorefractory colorectal cancer patients. Predictive testing strategies for the first model included HER-2 assay strategies based on IHC, FISH, both combined, or FISH confirmation of IHC-2+ for the breast cancer setting. The second model in the colorectal setting determined the health economic impact of the following strategies: KRAS testing, KRAS testing with subsequent BRAF testing of tumours with KRAS wild-type (KRAS/BRAF), cetuximab treatment without testing. Costs and effects of no trastuzumab or no cetuximab treatment of all breast or colorectal cancer patients, respectively, were used as reference values. For the review article, cost-effectiveness and cost-utility analysis of various treatment regimens for metastatic breast cancer were identified by literature and reference searches. The focus of the review was to critically assess the incremental cost-effectiveness ratios reported, the quality of the pharmacoeconomic evaluations and key modelling parameters included. Guidelines for critical appraisal of health economic studies built the basis of the appraisal.

Results. In the first project, FISH testing was the most cost–effective strategy with an incremental cost–effectiveness ratio (ICER) of € 12’245 per QALY gained compared to no trastuzumab treatment. The second model for the colorectal setting, determined KRAS/BRAF testing as the most cost-effective approach when compared to the reference strategy (ICER: € 67’779/QALY). All base-case results remained the preferred option in deterministic and probabilistic sensitivity analyses.

Pharamcoeconomic studies regarding metastatic breast cancer therapies presented diverse results. Clinical evidence does not propose one conventional chemotherapy treatment as favourable. However, cost-effectiveness ratios of cytotoxic drugs are generally favourable. Trastuzumab is currently the only antibody-based targeted drug established for metastatic breast cancer with diverse pharmacoeconomic outcomes.

Conclusion. Markers with a high predictive value such as HER-2 protein overexpression/ gene amplification or KRAS and BRAF gene-mutations can help identifying patients who are likely or unlikely to benefit from monoclonal antibody-based cancer therapies such as trastuzumab or cetuximab. In the early breast cancer setting, primary FISH testing with subsequent trastuzumab treatment of HER-2-positive cancers is a cost-effective and preferable approach. Despite substantial costs of predictive testing, it is economically favourable to identify metastatic colorectal patients with KRAS and BRAF wild-type status. Using state-of-the-art health economic methodology, we aimed at dealing, at least in part, with the current lack of economic data on this topic. Our results should be of relevance for oncologists, pathologists, and health policy makers.

Part I - Zusammenfassung

Hintergrund. Trotz eines enormen Fortschrittes in der Chirurgie und neuen Chemotherapeutika haben insbesondere Patienten mit fortgeschrittenem Krebsstadium im Allgemeinen eine schlechte Prognose. Monoklonale Antikörpertherapien, welche gegen molekulare Angriffspunkte, wie den epidermalen Wachstumsfaktor - Rezeptor (EGFR) oder den humanen epidermalen Wachstumsfaktor - Rezeptor 2 (HER-2) gerichtet sind, haben sowohl beim kolorektalen Karzinom wie auch beim Mamma - Karzinom einen wesentlichen Überlebensvorteil erzielt, jedoch auch das Gesundheitswesen mit erheblichen Mehrkosten belastet. Neue Studien haben gezeigt, dass nur jene Brustkrebspatientinnen mit einer HER-2 Protein Überexpression oder einer HER-2 Onkogen - Amplifikation von der monoklonalen Antikörpertherapie mit Trastuzumab (Herceptin®, Roche, Switzerland) profitieren können. Beim kolorektalen Karzinom werden bestimmte Mutationen in der Gensequenz der Proto-onkogene KRAS oder BRAF mit einer Resistenz gegen EGFR- Antikörper wie Cetuximab (Erbitux®, Merck AG) assoziiert. Den HER-2 Status bestimmt man derzeit durch ein immunhistochemisches (IHC) Verfahren oder die fluoreszierende In-Situ–Hybridisierung (FISH). Die Untersuchung des KRAS und BRAF Gen-Status erfolgt mittels DNA-Sequenzierung. Aus klinischer und ökonomischer Sicht ist es unumgänglich, jene Patienten zu ermitteln, welche tatsächlich von den Gentechnik-basierten, teuren Krebsbehandlungen profitieren können. Gesundheitsökonomische Daten zum Gebrauch von prädiktiven Tests für HER-2, KRAS oder BRAF sind begrenzt oder gänzlich fehlend.

Die vorliegende Arbeit untersuchte die Kosten-Effizienz von verschiedenen Teststrategien zur HER-2 Bestimmung bei der adjuvanten Antikörper–basierten Therapie von Brustkrebspatientinnen. Zusätzlich wurden Kosten und Nutzen der Mutationsanalysen von KRAS und BRAF bei therapierefraktären und metastasierten kolorektalen Karzinomen aus der Perspektive des Schweizer Gesundheitssystems untersucht. Schlussendlich wurden publizierte pharmakoökonomische Studien zu Therapiemöglichkeiten bei metastasiertem Brustkrebs kritisch bewertet.

Methodik. Ein Markov-Modell mit lebenslangem Zeithorizont wurde erarbeitet, um die Kosten (ausgedrückt in €) und den Nutzen (ausgedrückt in gewonnenen qualitätsadjustierten Lebensjahren, QALY) von prädiktiven Tests bei einer hypothetischen Kohorte von Brustkrebspatientinnen und Patienten mit metastasierendem Kolorektalkarzinom zu ermitteln. Das erste Modell verglich verschiedene Strategien der HER-2-Testung bei Brustkrebspatientinnen (IHC, FISH, IHC kombiniert mit FISH, oder Bestätigung der IHC-2+ Ergebnisse durch FISH). Das zweite gesundheitsökonomische Modell untersuchte prädiktive Tests bei Patienten mit kolorektalem Karzinom (KRAS Mutations-Analyse, zusätzliche BRAF Mutations-Analyse aller Patienten mit KRAS-Wildtyp (KRAS/BRAF), Cetuximab-Therapie ohne Testung). Als Referenz-Strategie dienten die Kosten und Effekte, welche aus einer Therapie ohne Trastuzumab beziehungsweise Cetuximab resultieren würden. Für den Übersichtsartikel wurden publizierte Kosten-Effektivitäts-Analysen (*cost-effectiveness*) und Kosten-Nutzwert-Analysen (*cost-utility*) zu verschiedenen Therapieverfahren bei Patientinnen mit metastasierendem Brustkrebs ermittelt und evaluiert. Einerseits wurden die berichteten inkrementalen Kosten-Effektivitäts-Verhältnisse, anderseits die Qualität und die zentralen Modell-Parameter der gesundheitsökonomischen Studien kritisch bewertet.

Ergebnisse. In der Studie zur HER-2-Testung von Patientinnen mit metastasiertem Brustkrebs war eine alleinige FISH Testung die kosteneffizienteste Strategie. Sie wies ein inkrementales Kosten-Effizienz-Verhältnis (*incremental cost-effectiveness ratio*, ICER) von € 12‘245 pro gewonnenem QALY auf, verglichen mit der Referenzstrategie (kein Trastuzumab). Die zweite Analyse favorisierte die kombinierte KRAS/BRAF-Testung. Das ICER betrug € 67’779 pro gewonnenem QALY, relativ zur Strategie ohne Cetuximab. Die Resultate der Basisanalyse blieben auch bei der Durchführung von deterministischen und probabilistischen Sensitivitätsanalysen stabil. Die in der Übersichtsarbeit identifizierten pharmakoökonomischen Analysen zur Behandlung des fortgeschrittenen Mammakarzinoms zeigten sehr unterschiedliche Resultate. Aus klinischer Sicht ergab sich keine Präferenz für eine Behandlung mit einer spezifischen konventionellen Chemotherapie. Grundsätzlich waren diese Behandlungen meist kostengünstig. Trotz unterschiedlichen gesundheitsökonomischen Ergebnissen ist Trastuzumab gegenwärtig der einzige auf ein molekulares Ziel gerichtete monoklonale Antikörper, welcher in dieser Indikation angewandt wird.

Bedeutung. Molekulare Marker mit guter Voraussagekraft, wie z.B. die Überexpression des HER-2-Proteins, Genamplifikation oder KRAS- und BRAF-Genmutationen, erlauben es zu untersuchen, ob Krebspatienten vermutlich auf spezifische, also gegen HER-2 bzw. EGFR gerichtete Therapien ansprechen werden. Es zeigte sich, dass beim adjuvanten Mammakarzinom eine alleinige HER-2-Bestimmung mithilfe von FISH die aus gesundheitsökonomischer Sicht geeignetste Strategie ist. Trotz substantieller Kosten der prädiktiven Tests ist es sinnvoll Patenten mit einem fortgeschrittenen kolorektalen Karzinom auf ihren KRAS- und BRAF-Status zu untersuchen. Evidenz zur ökonomischen Bedeutung der prädiktiven Testung bei Krebspatienten ist gegenwärtig nur begrenzt vorhanden. Mit Hilfe von gängigen gesundheitsökonomischen Methoden haben wir versucht, diese Lücke in der Literatur kritisch zu beleuchten und teilweise zu füllen, und so wichtige Informationen für Onkologen, Pathologen und Gesundheits-Politiker bereitzustellen.

Part II - Aims of the thesis

In an era of rising costs in cancer health care, it has become a necessity to allocate resources as efficiently as possible. Predictive testing helps to select the treatments patients will benefit most from. Additional costs of novel predictive tests in cancer patients have to be balanced against cost savings associated with avoiding treatment of patients who will predictably not respond to antibody treatment. However, there is no clear consensus on the most appropriate testing approach. In addition, only limited data on the economic consequences of assessing for markers like HER-2 or KRAS/BRAF is currently available. Therefore, the outline of this work was to:

1. Assess the costs and benefits of predictive testing for early breast cancer patients from a Swiss health care perspective. By using a life-long Markov state transition model, we determined the health economic influence of different HER-2 test assays prior to trastuzumab treatment: IHC alone, FISH alone, both tests combined or FISH confirmation of IHC-2+ status. Trastuzumab without predictive tests served as reference strategy.

2. Evaluate and summarise results of published, original cost-effectiveness analyses of cytotoxic and targeted non-chemotherapy regimens for metastatic breast cancer patients. In addition, the quality of reports, methodological and modelling issues will be broadly discussed.

3. Identify the costs and treatment related effects of predictive testing of chemorefractory metastatic colorectal cancer patients. The Markov model determined the pharmacoeconomics of the following test strategies prior to cetuximab treatment: KRAS testing alone, KRAS with subsequent BRAF testing of KRAS wild-types, and cetuximab treatment without testing.

Part III - Introduction

1. Essentials of pharmacoeconomic evaluations

1.1. Introduction

In health care as well as beyond, resources (time, facilities, equipment, money, knowledge) are scarce. Hence, choices have to be made. Informed decisions on whether resources should be spent for one or the other intervention, should be based on systematic analyses to identify the most appropriate alternatives. In the era of increasing health care costs, it is of uttermost importance to analyse and discuss the economic consequences of medical services. Health economics strives to find out which health services should be provided and consumed by whom. Key determinants are

- The *efficiency of allocation*, meaning the determination of the coverage and composition of the health care services;
- The *efficiency of production*, meaning the choice of the best available method to produce health care services;
- The realisation of the *health service allocation* at the lowest possible economic expenditures[1 2].

In view of the scarcity of resources, therapeutic, diagnostic and preventive processes are not only evaluated with regard to their effectiveness, but also to their economic characteristics, i.e. the ratio between resources utilised and associated effects. Health economic evaluation is a sub-discipline of health economics and mainly deals with the allocation of resources in the health sector. It is a scientific discipline that compares the value for money of one medical strategy to another. This is relevant for decisions on which services should be produced in response to different health problems, what kinds of interventions are needed to produce a certain level of health outcomes and who should finally be offered these services[3 4]. Several types of health economic studies can be distinguished. Study types and concepts used in economic evaluation are described in more detail in the following chapters.

Pharmacoeconomic evaluations determine the costs and effects of pharmaceutical interventions and I hereafter refer to all pharmaceutical-related health economic studies as “pharmacoeconomic evaluations”[2 3 5]. The use and success of a pharmaceutical is, at least in part, constrained by the result of pharmacoeconomic evaluations. In addition, pharmacoeconomic studies may help to evaluate research projects, to be used as a strategic marketing instrument, to discuss drug price cuttings or, to a lower extent, influence reimbursement decisions[3].

1.2. Basic concepts and terminology

The notion of opportunity cost plays a crucial part in ensuring that scarce resources are used efficiently[6]. Opportunity cost is the cost related to forgone value of the next best choice available to someone who has picked between several mutually exclusive choices[7]. It has been described as expressing "the basic relationship between scarcity and choice"[8]. Hence, the true cost of an intervention is what is given up to achieve it. Opportunity costs are not restricted to monetary or

financial costs: the real cost of output forgone, lost time, pleasure or any other benefit that provides utility should also be considered as opportunity costs[9 10]. In the health care setting, this approach demands for analysing the health gain yielded if resources are invested in the one or the other medical intervention. This means that resources saved by one intervention can be invested into another health care setting[5].

Health economic evaluations take into account both inputs (costs; expressed in monetary terms) and outputs (consequences; expressed in terms of monetary value or clinical efficacy) by generating, if applicable, an index of a cost-outcome ratio. Clinical efficacy is ideally expressed as quality-adjusted life-years (QALYs), a measure combining integration of survival and quality of life differences[1]. The approach of the study may be of prospective or retrospective nature.

Hereafter, key basic concepts of relevance for pharmacoeconomic evaluations are discussed.

1.2.1. Perspective of the evaluation

Given that medical services are mostly financed by several sources, the perspective of the analysis plays an important role. The appraisal of medical resources and hence the outcome of the study is mainly influenced by the chosen point of view. In the United Kingdom (UK) e.g., economic studies are conducted from the national health system (NHS) perspective which imply to assess how scarce resources may be allocated to maximise the health benefit within the NHS's budget. Evaluations from the social perspective include also costs or benefits other than the health care services which may occur from a medical intervention (Table 1)[11 12]. Hence, direct but also indirect costs are included. Direct costs covering medical (e.g. costs for health care service, medical staff salaries, drug costs, diagnostic tests, treating side effects and complications) and non-medical costs (costs for patient transportation, child care or home care service). On the other hand, indirect costs represent loss of added value as e.g. loss of productivity, loss of income, loss of leisure time or travel-costs to the hospital. Intangible effects (e.g. disease related pain and sufferings) are difficult to value in monetary terms. They impact, however, the patients' quality of life and are implicitly taken into account in the denominator of the cost-effectiveness equation if clinical effect is expressed in QALYs[3 5 13].

Evaluations may also take the perspective of the employer or the health insurance (covered services). The perspective of the studies has to be clearly stated. The choice of the perspective for pharmacoeconomic evaluations is given in some countries by binding recommendations[3].

	Patient	**Physician**	**Hospital**	**Payer***	**Society****
Direct medical costs					
Physician time	Yes	Yes	Yes	Yes	Yes
Other medical personnel time (e.g. nurse, technician)	No	Yes	Yes	Yes	Yes
Drugs	Yes	No	Yes	Yes	Yes
Medical devices	No	No	Yes	Yes	Yes
Laboratory tests	No	No	Yes	Yes	Yes

Direct non-medical costs					
Administration	No	No	Yes	Yes	Yes
Physical facility	No	No	Yes	No	Yes
Patient's travel costs	Yes	No	No	No	Yes
Temporary hired care-giver	Yes	No	No	No	Yes
Indirect costs					
Time off from work to visit physician	Yes	No	No	No	Yes
Time off work while ill and recuperating	Yes	No	No	No	Yes
Hire temporary household help while ill	Yes	No	No	No	Yes

*Third-party payer who reimburses physician for services rendered that are covered by an insurance scheme (private or public). **Sum of all perspectives.

Table 1. Costs included by using various perspectives. *Adapted from Meltzer MI, Lancet, 2001.*

1.2.2. The concept of marginal and incremental costs

Given that increased usage of medical interventions implies a decreasing marginal benefit, economic evaluation is a form of marginal cost analysis. Marginal costs are defined as changes in the total costs for producing an increase or decrease of one unit of a good or service. Pharmacoeconomic evaluations assess the difference in cost per difference in effect (incremental cost-effectiveness ratio; ICER). In other words, this form of analysis assesses the additional costs for producing a further unit of clinical effect, which meets the definition of marginal costs[3]. It should be noted, that the terms incremental and marginal costs unfortunately are sometimes used inconsistently in the literature.

1.2.3. The concept of discounting

Comparing different medical interventions often implies that costs and effects accumulate at diverse points in time. Frequently, the benefit of investing into a medical programme is only realised in the future[12 14 15]. Hence, future costs and health gains are weighted at a lower value than present ones[16]. The discounting of monetary values to the net present value of an investment leads to an economic tenable conclusion. Currently, most recommendations include annual discount rates between 3% and 6%, whereas 5% is the most common rate per year found in the literature[17]. The extent of how future costs and benefits are discounted in economic evaluations remains controversial. In order to assess the sensitivity of the obtained results, it is most reasonable to present the data discounted with different rates[3 5].

1.2.4. Time horizon

In a simulation model, the choice of the time horizon is regulated by the research question. It can range between a few weeks and numerous years to assess e.g. life expectancy. The time horizon should be at least long enough to cover all clinical effects and resource consumption of the studied alternatives, i.e. life-long when the disease is chronic or life-threatening[17].

1.3. Measuring health outcome

1.3.1. Assessing survival times

One possibility to measure the efficacy of a treatment in a clinical trial is by determining survival times. Usually, it is not possible to observe all patients until they die in a clinical study. Hence, the median overall survival is often the primary endpoint in clinical trials. The survival time is usually right-censored with few patients surviving much longer than the rest[18]. There are different methods available to evaluate the time to an event[18 19].

1.3.2. Utilities as a measurement of health outcome

Utilities are preference-based measurements of quality of life. Quality of life is expressed on a linear scale from zero to one, where the value one stands for perfect health and zero for death[1 20 21]. They are a form of evaluation which focuses mainly on the quality of health outcome gained or averted by health interventions. Utility values were developed as a tool for incorporating and rating multiple outcomes. This allows comparison of different diseases and health states and serves as a common denominator in health economic studies. The effectiveness of a treatment is converted to one common measurement unit, i.e. quality-adjusted life-year (QALY) gained which is a two-dimensional measure based on both life-prolongation (mortality) and quality of life (morbidity) (Figure 1)[1]. The QALY is obtained through weighting the time-span affected by a health outcome by the utility value of the resulting health status[22]. Utility can be regarded as summary measure of all clinical effects except survival time. Hence, it covers intangible effects, in a way.

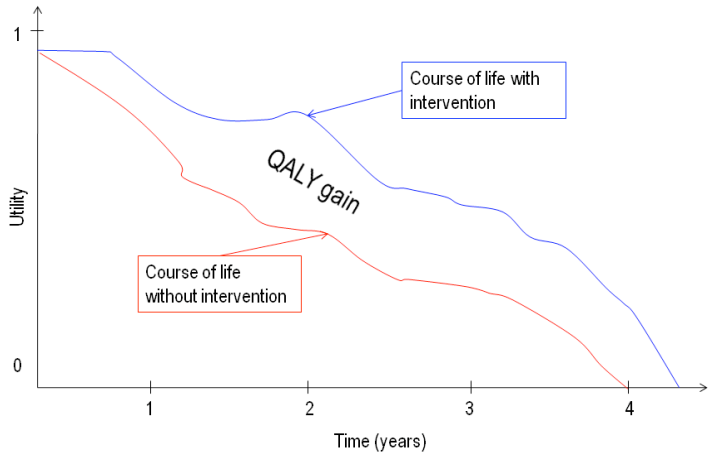


Figure 1. Exemplified figure of measuring QALYs. Area under the curve represents quality adjusted life-time.

Direct utility measuring techniques include “standard gamble”, “time trade-off” and “rating scale”. Gamble methods, based on game theory, ask patients to choose between a gamble and a certainty. The gamble represents the probability of dying because of a medical intervention treating e.g. breast cancer, whereas the certainty is given by living with the disease. The probability of the gamble gets varied until the point where individuals are indifferent between gamble and certainty[1 12]. The point of indifference corresponds to the patient’s utility.

By measuring indirect utility values, different subgroups of health states are rated (e.g. social opportunity, health perception and physical function). Indirect measurements are used to achieve short questionnaires which can be routinely utilised in the clinical setting. Table 2 exemplifies some utility values for different health states[20 23 24].

Health state	Utility value
Healthy	1.00
Mild angina	0.90
Colorectal cancer, primary chemotherapy	0.74
Stable cancer	0.62
Dialysis inpatient	0.56-0.59
Small cell lung cancer, 1 course of radiation	0.63
Depression	0.45
Progressive cancer	0.41
Blind or deaf or dumb	0.36
Terminal cancer	0.16
Dead	0.00

Table 2. Utility values of different health states.

1.4. Study types

Health economic evaluations can be of comparative or non-comparative nature. Different study types are discussed hereafter.

1.4.1. Cost-analysis

Cost-analyses are not comparative and usually measure direct costs of a medical intervention. The informative value is, however, limited as alternative strategies are lacking and indirect or intangible costs are dismissed. Nevertheless, cost-analyses may serve as initial evidence of the direct treatment costs of an intervention[3]. Their key implication is to generate input parameter for cost-effectiveness analyses.

1.4.2. Cost-of-illness analysis

Cost-of-illness studies are used as non-comparable, descriptive studies. Mostly, they assess direct but also indirect and intangible costs of an illness from a social perspective. Cost-of-illness analyses are targeted to estimate and reveal the economic total costs of a disease among the population. They give no information on how resources should be allocated to achieve gains in health outcomes. However, cost-of-illness studies give important information on the burden of disease that can be used as input parameters in economic evaluations. “Bottom-up” cost models prospectively accumulate data for each disease on an individual patients’ level. In contrast, the “top-down” approach breaks down the total expenditures on medical resources into parts attributable to each illness[1 25].

1.4.3. Cost-minimisation analysis

Cost-minimisation analyses compare the cost of different treatment strategies with no measurable differences in health outcome. Depending on the perspective of the study, this type of analysis evaluates the direct, indirect and intangible costs which lead to the selection of the treatment strategy

with the lowest costs. The main challenge of cost-minimisation analyses is the fact that major clinical effects must be shown to be the same for the comparators (Table 3)[3 26].

Study type	Measurement of benefits	Question posed
Cost minimisation analysis	Benefits found to be equivalent	Which is the most efficient way of achieving a given goal (or objective)? Or What is the most efficient way of spending a given budget
Cost effectiveness analysis	Natural units (e.g. life years gained)	
Cost-utility analysis	Healthy years (e.g. quality-adjusted life-years, healthy years equivalents)	
Cost-benefit analysis	Monetary terms	Should a given goal (or objective) be pursued to a greater or lesser extent?

Table 3. Overview of main types of pharmacoeconomic evaluations.

1.4.4. Cost-effectiveness analysis

Cost-effectiveness analyses calculate the monetary differences of various alternatives as well as the accompanied effects on the health state. Health outcomes may differ in between treatment alternatives. The health outcome is assessed e.g., as lives saved, cases treated or years of life saved. It is of outermost importance to measure the economic benefit in regard to life years saved for interventions which have a direct or indirect impact on the life expectancy. Life expectancy can be determined by the help of e.g. Markov models or life tables[3].

The ultimate aim of a cost-effectiveness study is assessing the ratio of the difference in cost to the differences in effects. The incremental cost-effectiveness ratio (ICER) compares the incremental difference of total costs to the incremental difference in benefits between two interventions (Equation 1)[1]:

$$ICER = \frac{Cost_{intervention} - Cost_{comparator}}{Effectiveness_{intervention} - Effectiveness_{comparator}} \quad (1)$$

The ICER provides information on the cost-effectiveness of an alternative treatment mode. Cost-effectiveness analysis is one type of study, serving as decision support on the allocation of resources which supply maximal health gains for a certain sum of resources. When costs and effects of two mutually exclusive treatments have to be compared, we can expect four possible results (Table 2)[1 27]. The result, namely costs and benefits, can be summarised using a so-called cost-effectiveness plane (Figure 2).

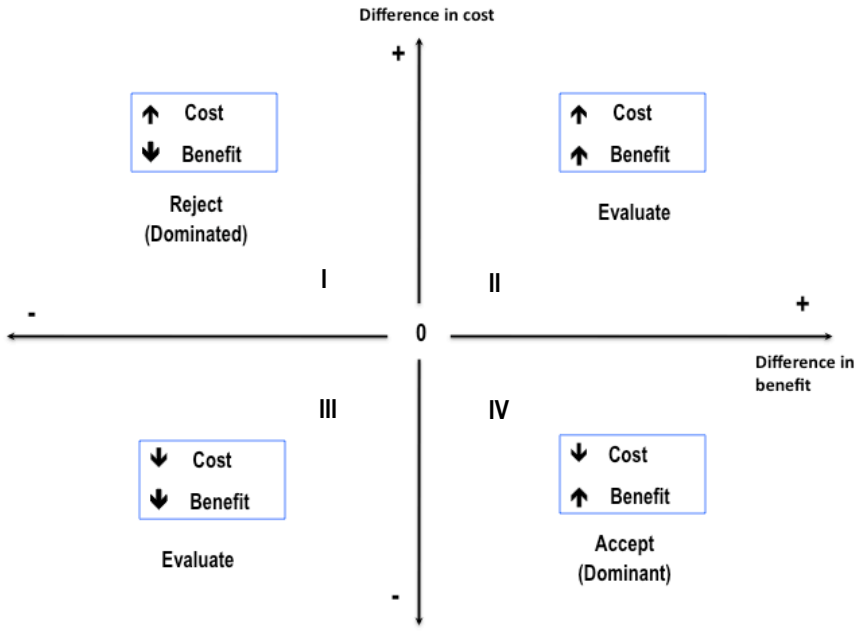


Figure 2. Potential results of a pharmacoeconomic evaluation of two different strategies.

The endpoint of the evaluation is not strictly defined through the treatment strategy but can rather be chosen by the researcher conducting the cost-effectiveness analysis. The favourable treatment relies on the willingness to pay for an additional health unit. The level of the willingness to pay is based on a supposed assessment of the monetary value of health gains among the society. If the ICER falls below the willingness to pay then the "new" treatment (treatment under investigation) is cost-effective and can be chosen (Figure 2; applied only for quadrant II). If the ICER falls above the willingness to pay then the "new" treatment (treatment under investigation) is assumed not to be cost-effective and the "old" treatment should be chosen. However, this benchmark only applies if the ICER falls into quadrant I (Figure 2). An ICER in quadrant III (negative ICER) implies that the "new" intervention is less effective but less costly, which is however, only acceptable provided that the loss of effects is minor.

1.4.5. Cost-benefit analysis

Cost-benefit analyses are economic measurements of consequences to create average or incremental ratios of cost per outcomes. This form of analysis determines both the intervention costs and the effects as monetary value of consumed resources and outcome, respectively[1]. Alternative treatment strategies may have complex or non-comparable health outcomes. Hence, this type of analysis allows to weigh against alternatives with dissimilar forms of effect measurements by assessing all intervention outcomes in monetary means (Table 3)[28]. Given this, different outcomes are converted into one common denominator which integrates all possible effects in a constant, reasonable and reliable manner. However, the monetary appraisal of treatment results is highly controversial, which makes cost-benefit analyses increasingly uncommon in the field of pharmacoeconomics. Alternatively, tools as e.g. willingness to pay or standard gamble techniques may be used to measure the individuals' willingness to pay to achieve an improvement in treating a disease[13].

1.4.6. Cost-utility analysis

Cost-utility analyses are a special form of cost-effectiveness analyses and accepted as “gold standard” among pharmacoeconomic evaluation, especially in Anglo-Saxon countries. Cost-utility analyses assess intervention costs in monetary values and health benefit in non-monetary units, namely quality-adjusted life-years (QALYs). This form of analysis is based on the fact that medical interventions influence the life quality of patients. Establishing the correct utility values according to each disease or health state is a key element (as described above)[1]. The outcome of the evaluation is the net cost per QALY gained. Hence, different cost-utility analysis results can be compared with each other, as they have a shared denominator (Table 3)[3].

1.5. Handling uncertainties

1.5.1. The concept of sensitivity analyses

Pharmacoeconomic models are necessarily simplified compared to the complex and dynamic reality. However, values and assumptions included in a model are subject to modification and error (e.g. prices, costs, resource use)[29]. Without a suitable reflection on uncertainties, the conclusion of an economic evaluation may not be judged as meaningful and robust[30 31]. Sensitivity analyses have two major objectives: investigating uncertainties in parameters as well as analysing different scenarios. The gained information allows confidence in recommending a strategy, if the preferred strategy is insensitive to parameter alterations. The range of parameter variation should be based on evidence and logic[17]. There are numerous ways of undertaking sensitivity analyses. Three of these have been applied in our study programmes and will be addressed in more detail.

Deterministic one-way sensitivity analysis

By varying one variable in the model by a certain degree, the impact of the change on the model’s result can be evaluated. For example, potentially influential parameters subject to statistical uncertainty (e.g. utility values) are varied within their 95% confidence intervals (CIs). The analysis can be repeated with different parameters. Consequently, the key parameters with the greatest influence on the result of the model can be identified[29].

Probabilistic multi-way *sensitivity analysis*

The likelihood that parameters reach a particular value is associated with uncertainty. In multi-way sensitivity analyses, several parameters subject to statistical uncertainty may be varied within one analysis. Probabilistic sensitivity analyses measure this uncertainty around the base case results by using e.g. 10’000 sets of parameter values randomly sampled from appropriate distributions which usually reflect the ranges of variation used in deterministic sensitivity analysis (Figure 3). This approach is known as second order Monte Carlo simulation[29]. Probabilistic sensitivity analyses serve as an appraisal instrument to measure the overall impact of parameter uncertainty on the results of a pharmacoeconomic evaluation.

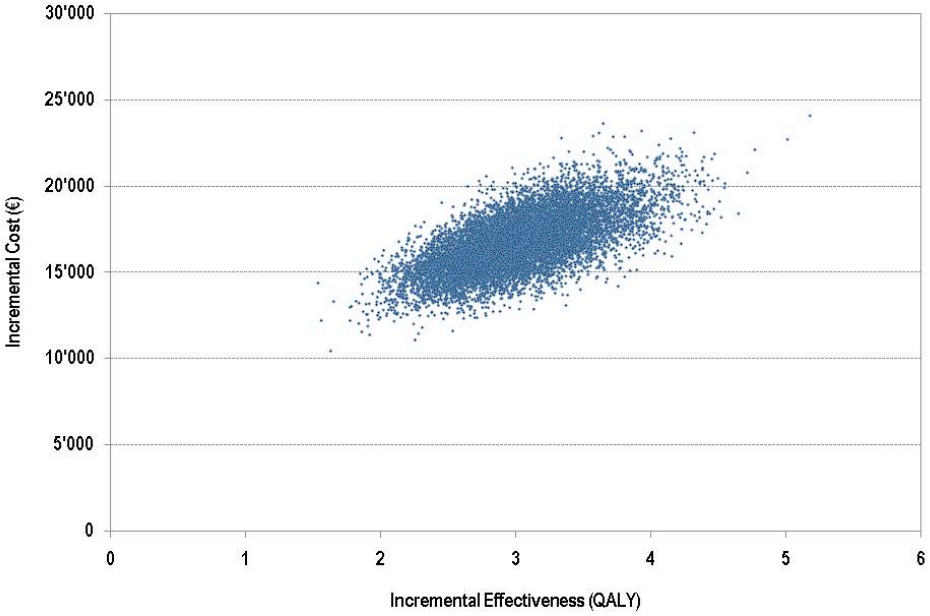


Figure 3. Cost-effectiveness scatter plot. The results of each set of parameter values are plotted on a chart showing the incremental cost and incremental effectiveness of the intervention in question. A large spread of the incremental results indicates an increased amount of uncertainty. Results with a tighter spread point towards results associated with a higher level of confidence.

Scenario-analyses

*S*cenario-analyses evaluate the influence of variations in specific parameters (e.g. the price of an intervention). They measure the range of a possible outcome if parameters have a higher or lower value. Several parameters may be varied within one analysis (e.g. to assess local characteristics), but scenario-analyses are not of probabilistic nature.

1.6. Collection and analysis of data

1.6.1. Within trial analysis versus decision analytic simulation

Pharmacoeconomic evaluations can either be conducted as within (or alongside) trial analysis or as decision analytic simulation. Within trial analyses replicate the health economic outcome of a clinical study. This means that they comprise of resource usage and of effects of the trial. The length of the analysis is the same as the trial itself. However, these assumptions have some shortcomings which should be noted. First of all, consequences of therapies mostly extend over a longer period than the trial period. Hence, the primary endpoint of a trial does not necessary reflect the required endpoint for health economic evaluation, which commonly has a life-long horizon if the decision to be taken may have life-long consequences[32]. In addition to this, the patient recruitment in clinical studies is highly selective due to strict inclusion and exclusion criteria. Furthermore, compliance can be assumed to be much higher than in daily routine where motivation and patient information may be less active. Generally, the number of medical and diagnostic interventions during a clinical trial can be presumed to be much higher compared to the standard clinical practice. Hence, all these assumptions do not directly represent everyday clinical reality. For validation reasons, clinical studies sometimes favour placebo as comparator, although this assessment does not always reflect the standard therapy[17 3]. Placebo, however, is not an option for being used as a comparator in pharmacoeconomic evaluations,

when standard care is available. The choice of the comparator is still an open discussion and needs to be determined individually as the case arises. There is no clear answer, whether the most widely used or the “gold standard” should be used as an adequate reference[1].

Modelling has become a widely used tool in the economic evaluation of new interventions in the health care setting[33]. Modelling is required when clinical outcomes have to be extrapolated beyond clinical trial data, final outcomes of intermediate measures have to be transformed, data from different sources have to be used to carry out a decision analysis, or trial or review data have to be utilised to reflect the outcome of different clinical settings[17 34]. Simulation models take advantage of different sources of information to obtain data on the epidemiology, costs and effects to simulate different treatment strategies over a period of time[1]. In brief, they simulate the reality in a simplified way as unimportant details are omitted but key information is kept. Generally, simulation models are developed on the basis of logical and objective appraisal of intervention and outcome and correspond to random, evolving processes[34]. Nevertheless, these models may miss key information seen in the real world. Hence, the structure and content of a model has to be justified, revealed and validated using a number of methods, e.g. sensitivity analyses[35]. Most commonly, Markov cohort models, individual based simulation models or decision tree models are used for those simulations. Markov models and decision tree models will be discussed in greater detail in the following chapter.

Noteworthy, within trial analyses and modelling are not mutually exclusive evaluation techniques. Frequently, both assessments are combined meaning that trial data serve as basic assumptions which are modelled beyond what has been observed in a set of direct observations. Furthermore, trial data may be corrected or adjusted to achieve a more accurate reference to the clinical routine.

1.6.2. Decision analysis models

Decision analysis models serve as a quantitative clinical epidemiology instrument to measure supposed risks, benefits, utilities and costs related to the different treatment options. To a certain degree, modelling with decision analyses can support, substitute or revoke results obtained from clinical trials. Decision analysis models are also used for the economic evaluation of health care technologies[36].

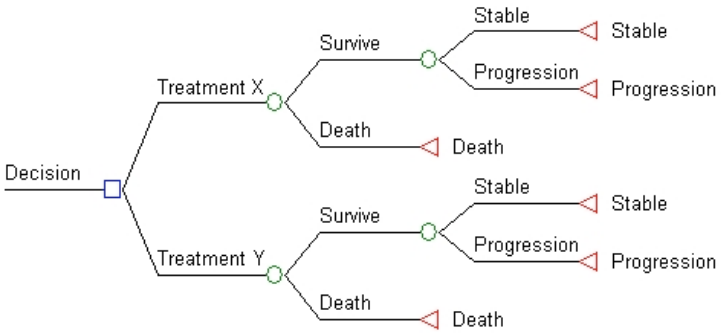


Figure 4. Exemplified decision tree (□ Decision node, ○ probability node)

Decision trees

Decision trees reproduce economical, clinical, therapeutic and diagnostic processes in a simplified way[3]. For example, they start with a decision (e.g. treatment X or treatment Y), and trace out all possible pathways and effects (e.g. costs or health benefits) which accumulate over a period of time (Figure 4)[1 3]. In health economic applications, decision trees might give an answer of how money should be invested (e.g. in intervention A or intervention B).

Markov models

Some diseases are characterised by recurring disease states which indicate the need for modelling the dynamic process of a constant risk of disease recurrence[1]. In this case, Markov models may be used. They are time sensitive state transition models which simulate long-term processes (e.g. chronic diseases)[34]. Analyses of Markov models can be classified into two commonly-used methods:

1. **'***Cohort analysis' (expected value calculation)*

In a 'cohort analysis', the percentage of a hypothetical cohort in a particular state during a cycle is multiplied by the costs and effects which are associated with that state. At the beginning, all individuals start in the same or in different health state (e.g. disease free, regional recurrence or progressive disease). During each cycle, individuals can be situated in only one of the finite sets of mutually exclusive states (Figure 5). The time period of a Markov model is composed of equal cycles. The change from one state to another is defined by the transition probabilities of passing into that particular state[1]. For each state, different costs and effects are set per cycle a person resides in. The final values are summed up over all states and cycles which were included in the model[37]. Cohort analyses are restricted in the way of their memory. This refers to the chance of moving from one health state to another regardless of the patient's previous history[34 38 39]. This means that moving from one state to another is not regulated by previous states a patient may have experienced. This "memoryless" characteristic may, however, be avoided by using different techniques (e.g. first order Monte Carlo simulations)[34 38]. However, in many practical situations, cohort analyses provide as much information as Monte Carlo simulations.

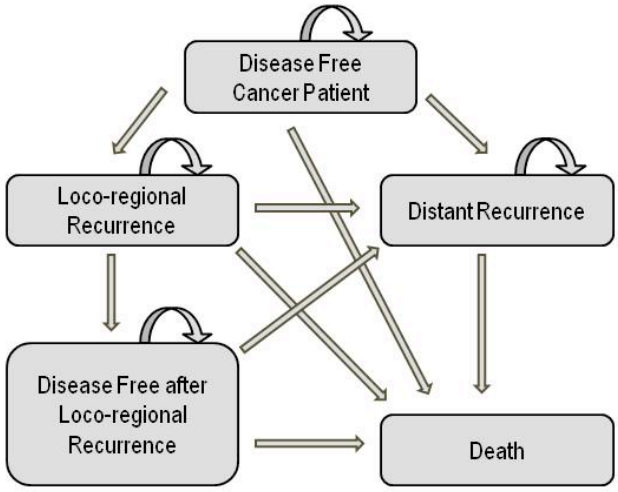


Figure 5. Exemplified bubble-diagram of a cancer Markov model.

In our programme, the Markov model was constructed based on a cohort analysis.

2. *First order Monte Carlo simulation (discrete event simulations)*

Discrete simulations represent a large number of patients which are followed through the model individually by following a randomly varied path based on transition probabilities. The final results are average estimates of numerous trials[34].

1.7. Assessing quality aspects of health economic studies

The usage of clinical trial data with poor quality or biased results as well as inadequately designed economic models are a major concern in pharmacoeconomic evaluations. Guidelines have been established to increase the validity, robustness and reliability of health economic evaluations. To guide critical appraisal of health economic studies, a number of checklists were developed[17 40]. In principle, two primary goals are strived for: the risk of bias in the underlying effectiveness study results and the methodological quality of the economic evaluation is assessed (Table 4, originally published by Drummond et al, BMJ 1996)[17 40]. In some countries, there are even binding guidelines how such studies have to be conducted (e.g. Australia)[41]. Our analyses have been conducted based upon the guidelines by Drummond et al[17].

Study design	The research question is stated
	The economic importance of the research question is stated
	The viewpoint(s) of the analysis are clearly stated and justified
	The rationale for choosing the alternative programmes or interventions compared is stated
	The alternatives being compared are clearly described
	The form of economic evaluation used is stated
	The choice of form of economic evaluation is justified in relation to the questions addressed
Data collection	The source(s) of effectiveness estimates used are stated
	Details of the design and results of effectiveness study are given (if based on a single study)
	Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)
	The primary outcome measure(s) for the economic evaluation are clearly stated
	Methods to value health states and other benefits are stated
	Details of the subjects from whom valuations were obtained are given
	Productivity changes (if included) are reported separately
	The relevance of productivity changes to the study question is discussed
	Quantities of resources are reported separately from their unit costs
	Methods for the estimation of quantities and unit costs are described
	Currency and price data are recorded
	Details of currency of price adjustments for inflation or currency conversion are given
	Details of any model used are given
	The choice of model used and the key parameters on which it is based are justified
Analysis and interpretation of results	Time horizon of costs and benefits is stated
	The discount rate(s) is stated
	The choice of rate(s) is justified
	An explanation is given if costs or benefits are not discounted
	Details of statistical tests and confidence intervals are given for stochastic data
	The approach to sensitivity analysis is given
	The choice of variables for sensitivity analysis is justified
	The ranges over which the variables are varied are stated
	Relevant alternatives are compared
	Incremental analysis is reported
	Major outcomes are presented in a disaggregated as well as aggregated form
	The answer to the study question is given
	Conclusions follow from the data reported
	Conclusions are accompanied by the appropriate caveats

Table 4. Checklist for the appraisal of the quality of health economic studies. *Adapted from Drummond et al, BMJ, 1996.*

1.8. Practical use of economic evaluations

There is an implicit assumption that decision makers should prefer those technologies with the lowest costs but the highest gain in effects. Hence, the primary question is how they can most effectively spend resources to extend quality-adjusted life-time or an alternative measurement of clinical effect[42]. Given that the choice of an intervention follows the "rational choice" principle and the alternative with the maximal benefit or, respectively the minimal cost is chosen. Medical interventions with better health outcome at lower costs are evidently accepted. If interventions indicate improved effects at higher costs, the decision is less clear and needs further decision support[43]. It should be taken into account that the term "cost-effective" and "cost-savings" may not be used interchangeably. Cost-saving interventions decrease costs, whereas cost-effective procedures provide an adequately large advantage in contrast to their costs, but may not save money[44].

The affordability of health care may be examined by budget-impact analyses, which supply information on how a change in the mix of pharmaceuticals will influence the course of health care spending in a certain disease. Budget-impact analyses evaluate the financial implications of establishing and diffusing medical innovations within an explicit health care setting. They are working in parallel to cost-effectiveness studies and may be placed complementary to them for guiding the allocation of health care resources[45].

1.8.1. Cost-effectiveness thresholds

In a number of countries, the decision of accepting or rejecting an intervention is based on the willingness to pay for a gained unit of health benefit (e.g. measured as QALY). In the Anglo-Saxon region cost-utility analyses are regarded as the "gold standard" for health economic evaluations. Based on the reimbursement decision and recommendations by national government agencies, cost-effectiveness thresholds vary between countries. Usually, a medical intervention is considered as justified, if it remains below US$ 20'000, US$ 50'000 (€ 39'700) or US$ 100'000 (€ 79'300) per QALY or life year gained (LYG)[46]. In North America, a threshold of US$ 50'000 per QALY gained is usually accepted, although in the real world, for new medical interventions a much higher threshold is mostly applied (US$ 100'000/QALY)[47]. Recently, Braithwaite revealed that cost-effectiveness thresholds of US$ 50'000/QALY are not consistent with present resource allocation decisions among the population of the United States of America (USA)[48]. They estimated a social willingness to pay between US$ 109'000/QALY (€ 86'500/QALY) and US$ 297'000/QALY (€ 235'600/QALY) when considering the impact of health care on quality as well as quantity of life. In the UK, the decision rule for the acceptability of cost-effectiveness studies ranges according to the National Institute of Clinical Excellence (NICE) typically between € 23'322/QALY (£ 20'000/QALY) and € 34'983/QALY (£ 30'000/QALY)[49] [50]. Although not legally binding, this threshold has been more or less officially communicated. However, the NICE thresholds are stricter than the limits usually accepted in Switzerland.

Cost per LYG and QALY gained are not exchangeable. Usually, costs per QALY indicate higher values than costs per LYG do. Moreover, cost-effectiveness varies according to the target population. Usually, the cost-effectiveness ratio improves within high-risk groups.

1.9. Implication for our cancer models

1.9.1. Study type

In cancer patients, the quality of life is of utmost importance with regard to the clinical outcome. Different test assay strategies, as applied in our models, may indirectly influence both the mortality and morbidity of cancer patients by the treatment strategy chosen. In my case, cost-utility analyses have been thus determined as the most appropriate study type to measure the health economic impact of applying diverse predictive test approaches in breast and colorectal cancer patients. In addition, this type of study is widely used when assessing costs and benefits of new cancer drugs or interventions.

1.9.2. Design characteristics

The first breast cancer Markov model was created with cycle lengths of one year, as most health economic models in the adjuvant breast cancer setting have used a one-year cycle length. The time horizon was life-long. This approach ensured that the simulation model included all stages breast cancer patients may undergo during their remaining life. Given that the second Markov model covered advanced colorectal cancer patients, the selected cycle length was shorter, namely one month. The model horizon was life-long also.

Both Markov models are based on data from randomised clinical trials while especially utility values and information on medical resources have been adapted to establish a reference to the clinical reality.

2. The burden of disease of breast and colorectal cancer

Cancer is the leading cause of death all over the world. According to the World Health Organization (WHO), more than 7.6 million deaths were accounted in 2005. Colorectal and breast cancer are one of the main types of cancer, leading to around 639'000 and 519'000 deaths per year, respectively[51]. However, overall life expectancy between 1988 and 2000 for cancer patients has improved. Increases in survival of 3.6 years and 1.7 years were reported for breast and colorectal cancer, respectively[52].

2.1. Incidence, prevalence and mortality

2.1.1. Colorectal cancer

Colorectal cancer is a considerable cause of morbidity and mortality in the Western world including Switzerland. In fact, more than 1 million new cases are identified worldwide each year[51]. The yearly average of Swiss incident cases for colorectal cancer (C18-20) is about 4'029 (period 2003-2007), while the rate of new cases has risen by a factor of 1.3 during the last thirty years[53]. This trend was also visible in countries outside Switzerland[54]. The Swiss one-year prevalence is higher for men than for females with 2'256 and 1'646, respectively[55]. Patients in the age group of 50 years and above are largely affected by this type of cancer (94% of all cases)[53].

Initial therapies of early cancer stages often end up in appearance of recurrent local or metastatic disease which finally leads to death from colorectal cancer. About 25% of all cancer cases develop metastases[56 57]. However, colorectal cancer-related deaths indicate a falling number[58]. In Switzerland, approximately 1'809 cancer patient die each year[53].

2.1.2. Breast cancer

During the period of 2001-2004, the number of new breast cancer cases summed up to 21'141 in Switzerland. The highest incidence was found in the age group of 50 to 69 years old females (10'380)[59]. In 2002, 1'404 deaths were recorded among Swiss females [55]. Due to the augmented performance of screenings, however, the incidence of cancer has increased[60]. In fact, in Switzerland the number of new female breast cancer cases has increased by 1.5 between 1993 and 2007 (yearly average: 3'460 (1'993-1987) and 5'244 (2003-2007))[53].

Despite the advantages in breast cancer therapies, the metastatic cancer is still not curable [61]. But, breast cancer mortality rates have decreased in recent years[62 63]. This fact can be mainly attributed to early detection, efficacious surgical procedures and the ameliorated chemotherapeutic or radio-therapeutic cancer treatments. Early detection is also associated with a high cure rate for early-stage cancer patients.

2.2. Cost-of-illness

The trend of declining cancer deaths and increasing incidence is a great progress in cancer treatment, but has also increased treatment-related expenditures. The increase in health care expenditure reflects the raising volume and intensity of the use of services provided to patients[64]. In cancer care, these interventions include screening, diagnostic tests, medication, surgery, radiation therapy and secondary, supportive or palliative care[65]. Cancer drug costs have attracted growing attention due to the high prices of new drugs which exceed frequently the cost-effectiveness thresholds[66 67]. Arguments for these high costs may be the risks for development and production taken by the pharmaceutical industry and the significant benefit for cancer patients[68]. In European countries like France or Germany, but also in the USA, it is estimated that cancer care expenditures account for about 5% of the overall health care costs[69]. The financial impact of cancer is substantial, not only for society, but also for patients and their families[64]. In fact, 25% of insured American cancer patients claim that they spent most or all of their savings for the cancer treatment, while 33% argue they are not able to pay the cancer invoice[70]. For cancer patients, the survival benefit been found to be worth around half of the full income. Even patients with a very low salary would pay up to 40% of their entire earnings for gains in survival[52].

Life-time costs of cancer patients vary depending on cancer site, stage of diagnosis, age and treatment[71-74]. In the colorectal setting, estimated mean net annual costs range between US$ 5'341 (€ 4'316) and US$ 11'614 (€ 9'386) per patient[73]. For Stage IV patients, the excess lifetime cancer-related health care costs are higher and represent approximately US$ 30'794 (€ 24'885.19) per year[71]. The estimated annual direct and indirect costs account for about US$ 454 million (€ 353 million) in Switzerland (Table 5)[75]. The per-patient costs for the initial breast cancer treatment was estimated at

US$ 10’813 (€ 8'738), for continuing care at US$ 1’084 (€ 883) and for terminal care at US$ 17’886 (€ 14'454)[74]. Nevertheless, direct and indirect costs are dependent on disease stage. Recent numbers from a Belgian breast cancer study presented per patient costs of about € 107’456 over a six year period. Indirect costs measured as productivity loss accounted for 89% of the total costs[76]. In Switzerland, colon cancer patients are estimated to lose approximately 263’400 workdays per year (Table 5)[75]. Hence, indirect costs of illness are major cost-drivers. The introduction of new medical innovations which help to prevent, identify and treat cancer patients may, therefore, enhance the direct cost at short-term, but do also have a main influence in reducing the productivity loss in those patients.

	Switzerland	**Europe***	**USA**
Breast Cancer (per year)			
Breast cancer incidence	4’954	282’600	210’000
Cancer related doctor visits	601’200	44.6m	24.4m
Cancer related hospitalisation	8’300	681’900	337’600
Cancer related workdays lost	375’750	27.9m	27.9m
Direct medical costs	US$ 107m	US$ 6’096bn	US$ 4’530bn
Indirect medical costs	US$ 347m	US$ 23’378bn	US$ 10’775bn
Colon Cancer (per year)			
Colon cancer incidence	4’418	287’437	165’690
Cancer related doctor visits	343’500	25.51m	13.97m
Cancer related hospitalisation	5’800	785’900	155’400
Cancer related workdays lost	263’400	19.56m	10.71
Direct medical costs	US$ 204m	US$ 15.129bn	US$ 8.285bn
Indirect medical costs	US$ 59m	US$ 4.383bn	US$ 2.400bn

*25 Member States and Switzerland (2006)

Table 5. Estimated annual burden of breast and colon cancer. *Table adapted from Roche Kiosk, http://www.health-kiosk.ch/cancer.htm.*

3. Predictive markers in oncology

3.1. Overview

3.1.1. Predictive versus prognostic markers

Prognostic and predictive markers have two distinct roles with regard to treatment decisions in cancer care. In principle, prognostic markers assess whether a patient needs a treatment, whereas predictive markers identify which treatment will be the most appropriate one. Both markers may characterise the patient or the nature of the tumour[77]. Prognostic factors foresee in an objective and independent manner the clinical outcome of a patient as e.g. patients at risk of relapse or with an overall bad

prognosis. On the other hand, predictive markers intend to forecast how patients may respond to a particular treatment agent[78]. Often, they are linked to tumour sensitivity or resistance to the medical intervention. Molecular markers may have both prognostic (e.g. poor overall prognosis) and predictive implications (e.g. response to monoclonal antibody treatment), as is the case with HER-2[77].

3.1.2. Predictive and prognostic markers in the clinic

Monoclonal antibodies have raised hope in the treatment of cancer. Deeper knowledge of the molecular pathogenesis has prompted the progress of specific targeted therapies, including monoclonal antibodies. These agents have been demonstrated to significantly increase the response rate, progression free survival time and overall survival. However, targeted therapies do not fit into all patient profiles. Among patients not harbouring a particular gene mutation, gene amplification or overexpression of proteins, the probability of response to the targeted treatment is minor[78]. It is crucial to identify reliable prognostic factors as well as biological markers which might have the capacity to predict the response of a treatment. Diagnostic tests have to assure that specific evaluation criteria are achieved. Key requirements for diagnostic and predictive tests are accuracy, reproducibility, precision but also low costs[79].

3.2. Human epidermal receptor 2 in breast cancer

3.2.1. Biology of HER-2 pathway

Human epidermal growth factor (HER) 2 (HER-2, ErbB2/neu) belongs to the transmembrane receptor tyrosine kinases which are involved in controlling cell growth, survival, differentiation and mitigation[80] [81]. HER-2 is encoded by the ErbB2 gene which is located on the long arm of the human chromosome 17 ((17q21-q22)[82]; CEP17). ErbB2 receptors are monomers composed of 1'233 amino acids (185 kD) and are mainly expressed in tissues of epithelial, mesenchymal and neutronal nature[83] [84]. The ErbB sub-family includes besides HER-2 three other receptors, namely HER-1, HER-3 and HER-4[85].

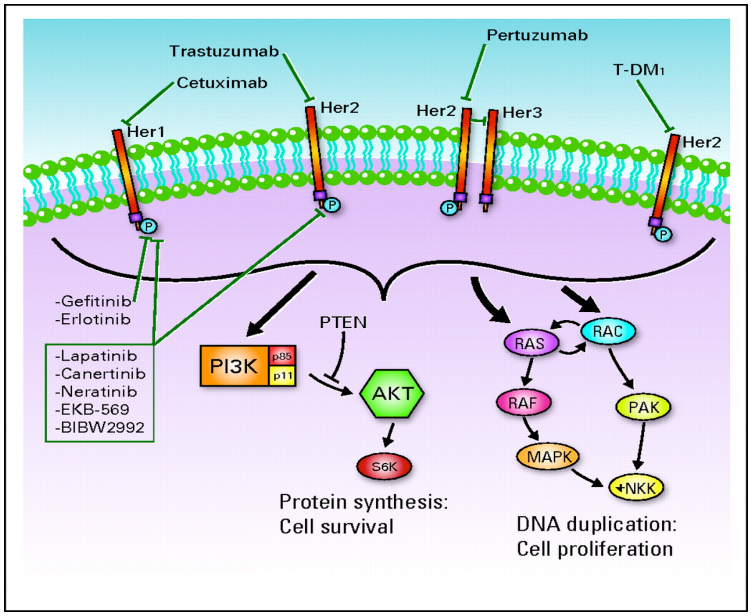


Figure 6. Signalling pathways of human epidermal growth receptor family members. Four homologue receptor compose the EGFR family, namely ErbB1 (EGFR/HER-1), ErbB2 (HER-2/*neu*), ErbB3 (HER-3), and ErbB4 (HER-4). After ligand binding to EGFR, the ErbB receptor gets activated by homo or hetero-dimerisation. This process leads to phosphorylation of catalytic substrates of key signalling pathways regulating apoptosis, protein synthesis, and cellular proliferation (e.g. through MAPK pathway or PI3K/AKT/PTEN family). *Adapted from Alvarez, R. H. et al. J Clin Oncol; 2010.*

HER proteins are present at the plasma membrane and form a homo-dimerisation (of two identical receptors) or hetero-dimerisation (of two different receptors), when bound by a ligand. In contrast to other ErbB sub-family members, HER-2 is capable of signalling constitutively without being activated by a ligand[86].

This procedure induces kinase activation and trans-autophosphorylation of the receptor. With help of adaptor proteins, the receptor is connected to several downstream pathways controlling survival and proliferation (e.g. through phosphatidylinositol triphosphate kinase (PI3K) and RAS/RAF/mitogen-activated protein kinase (MAPK)) (Figure 6)[84 87].

3.2.2. HER-2 protein as a molecular target

It is estimated that HER-2 gene amplification or protein overexpression is found in about 20% to 25% of breast cancers[88-90]. Aberrant HER-2 signalling is linked to an inhibition of apoptotic stimuli through a deregulation of the PIK3-kaskade which leads thus to an aggressive tumour with poor clinical prognosis[86 89 91]. In addition to that, HER-2 overexpression is linked to responsiveness to cytotoxic chemotherapy but is resistant to tamoxifen antioestrogen therapy[92 93]. Blocking HER-2 with targeted therapies inhibits the activity of those survival pathways and induces cell apoptosis. Therefore, HER-2 exhibits a convenient molecular target for specific therapies.

Lapatinib (Tyverb®, GlaxoSmithKline, London, UK) is a small-molecule inhibitor of the tyrosine kinase activity of both HER-1 and HER-2 (Figure 6)[94]. In combination with chemotherapy, lapatinib is effective in locally advanced or metastatic HER-2 overexpressing cancer patients[87 95]. Trastuzumab (Herceptin®, Roche, Switzerland) is a monoclonal humanised antibody targeted against the extracellular domain of HER-2 (Figure 6). The exact mechanism of the anti-tumour activity of trastuzumab is not yet fully understood. However, from preclinical research, it is proposed that extracellular (through antibody-depended cellular cytotoxicity) or intracellular actions like the inhibition of signal transduction and cell cycle arrest, inhibition of proteolytic cleavage, inhibition of tumour angiogenesis or inhibition of DNA damage repair are the mechanism of action[86]. In HER-2 positive breast cancer patients, the treatment with trastuzumab is clearly associated with improved clinical outcome in both the invasive and early disease state[96-101].

3.2.3. Testing for HER-2

Three different test methods to assess the HER-2 status are currently validated and approved by the Food and Drug Administration (FDA): immunohistochemistry (IHC), fluorescence in situ hybridisation (FISH) and chromogenic in situ hybridisation (CISH)[79 102 103]. Some emerging HER-2 testing methods like HER-2 silver in situ hybridisation (SISH) which detect HER-2 gene and chromosome 17 using a standard bright-field microscope or reverse-transcriptase polymerase chain reaction (RT-PCR) for HER-2 gene amplification became, however, not yet firmly established in the laboratories of pathologists[104 105]. In our analysis the techniques most frequently used were focused (IHC and FISH).

Immunohistochemistry

Immunohistochemistry (IHC) determines the receptor overexpression by measuring the density of HER-2 receptors on the tumour cell surface[106]. HER-2 proteins are stained by HER-2 antibodies and a chemical detection method on formalin-fixed, paraffin-embedded (FFPE) tissues. Two immunohistochemical assay methods are approved by the FDA (HercepTest™; DAKO, Carpinteria, CA; and Pathway; Ventana Medical Systems, Tucson, AZ). The test result is visible by bright-field microscopes and interpreted based on a specially devised scoring system. Both the intensity and the

pattern of the membrane staining are taken into account when interpreting the slides (Table 6)[107 108]. Cancer cells with a score of 0-1+ are not qualified e.g. for trastuzumab treatment, whereas patients with 3+ tumour cells are eligible for antibody therapy targeted against HER-2. Equivocal results (2+) need further assessment by e.g. FISH[102]. The test result is highly subjected to inter-observer variability.

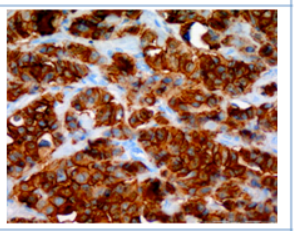
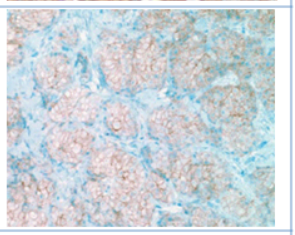
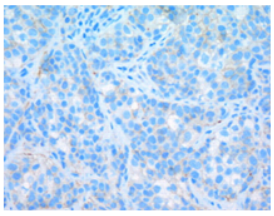
Score		IHC HER-2 protein expression	MAb therapy	IHC staining (x200)
Positive	3+	- Uniform intense membrane staining of > 30% of invasive tumor cells	Yes	
Equivocal	2+	- Complete membrane staining - Intensity: nonuniform or weak - Obvious circumferential distribution in ≥ 10% of cells	Needs further assessment	
Negative	0 or 1+	- No staining or - Weak, incomplete membrane staining in any proportion of tumour cells	No	

Table 6. Scoring system and pathology of IHC HER-2 testing. IHC, immunohistochemistry; MAb: monoclonal antibody. *Figures adapted from Hofmann et al, J Clin Pathol, 2008 and Striebel et al, Am J Clin Pathol, 2008.*

Fluorescence in situ hybridisation (FISH)

Fluorescence in situ hybridisation (FISH) is a method which identifies the HER-2 gene amplification by assessing the copy numbers of the HER-2 gene in the nuclei of the cells in combination with the copy number of chromosome 17 centromere (CEP17) in FFPE tissues[104]. The ratio of the number of HER-2 signals to the number of CEP17 signals in the nuclei of twenty cancer cells yields the FISH test result. In HER-2 positive tumour cells, two or more HER-2 gene copies per chromosome 17 have to be found (gene amplification) (Table 7)[79 107-109]. According to the American Society of Clinical Oncology and the College of American Pathologists (ASCO-CAP) guidelines, the cut-off ratio for HER-2/CEP17 for normal cells is below 1.8 (or less than 4 HER-2 gene copies per nucleus), while HER-2 positivity was defined as a HER-2/CEP17-ratio greater than 2.2 (or more than 6 HER-2 gene copy numbers per nucleus)[79]. The range between 1.8 and 2.2 (or 4-6 HER-2 copy numbers per nucleus) was determined as equivocal for HER-2 amplification, given 2% of breast cancers fall in this interval[79 110] (Table 7). Currently, three specific FDA approved FISH-assays are available (PathVysion; Abbott Laboratories, Abbott Park, IL; INFORM; Ventana Medical Systems, Tucson, AZ; and PHarmDx; DAKO, Glostrup, Denmark). The test results are visible through a fluorescence microscope.

FISH testing is a quantitative and objective method but time-consuming and hence, an expensive technique. Test results can be influenced by the thickness of the tissue section. The interpretation and recognition of the invasive component require experience[104].

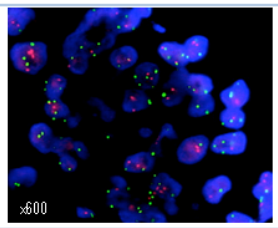
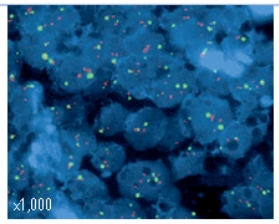
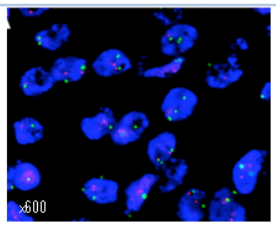
Score	FISH ratio (HER-2:CEP17) or HER-2 gene copy number per nucleus	MAb therapy	FISH staining
Positive	- HER-2/CEP17 ratio > 2.2 or - HER-2 copy number > 6	Yes	
Equivocal	-HER-2/CEP17 ratio1.8 - 2.2 or - HER-2 copy number 4-6	Needs further assessment	
Negative	-HER-2/CEP17 ratio < 1.8 or - HER-2 copy number <4	No	

Table 7. Scoring system and according image for HER-2 assessment by FISH. CEP17, chromosome 17; MAb, monoclonal antibody. *Figures adapted from Hofmann et al, J Clin Pathol, 2008 and Striebel et al, Am J Clin Pathol, 2008.*

3.2.4. Which test is the most appropriate one?

Regardless of a long history of HER-2 testing in breast cancers, there is still no consensus what test represents the best assessment („gold standard“) of the HER-2 status. Both assay methods have technical shortcomings resulting in different sensitivities and specificities. The debate is still ongoing regarding what is the best test to assess the HER-2 status, because there are contradictory results reported in the literature comparing HER-2 status determined by FISH or IHC assays in FFPE tissues. However, standardisation of IHC in FFPE tissue samples is difficult to achieve due to numerous pre-analytical problems and a high subjectivity in the interpretation of IHC samples. High concordance between IHC and FISH tests is achievable, but this is mostly dependent on the methodology, instrumentation and experience of the laboratories carrying out the tests[111]. It was shown that concordance rates between IHC and FISH tests range between 80% and 90% and this implies the production of significant numbers of false negative tests, which may have a dramatic consequence for the affected patients[111 112].

In addition to these primary criteria, secondary considerations, such as costs are helpful in selecting different assay strategies. Although the ASCO-CAP guidelines recently recommend IHC assays for initial evaluation of the HER-2 status, primary use of FISH in initial testing is also discussed. Higher reproducibility and more accurate assessment of the HER-2 status are strong arguments for FISH, but

it has been argued that FISH is more expensive, time consuming and require more expertise than IHC[113]. IHC is limited in terms of conditions of the test procedure including time to fixation, fixation duration, processing, denaturation, heating, antigen retrieval, the staining procedure used, and the interpretation of staining[114]. Furthermore, detecting HER-2 overexpression at the protein level may imply inadequate conclusions.

3.3. KRAS and BRAF in colorectal cancer

3.3.1. Biology of the KRAS/BRAF- pathway

The activation of EGFR is used by tumour cells as a key element for independent proliferation and cell survival. When a ligand binds to the extracellular domain of the receptor, the receptor dimerises and triggers its enzymatic activity followed by the phosphorylation of the intracellular domain. Through relocalisation to the plasma membrane, cellular effectors bind to the phosphorylated residues of the intercellular part and initiate cell growth, development and cell functions[115 116]. Intracellular key mediators of the EGFR signalling include the small G-protein RAS (KRAS), the protein kinase v-raf murine sarcoma viral oncogene homolog B1 (BRAF), phosphatidylinositol 3'-kinase (PI3K)/AKT, and the JAK-STAT pathway[115].

The initiation of the KRAS protein can induce BRAF protein activation. BRAF has a known role in triggering signal transduction through the mitogen-activated protein kinases (MAPK) (Figure 7)[115]. MAPK translocates to the nucleus and induces the expression of genes involved in cell survival[117]. Hence, the pathway through RAS/RAF/MAP has been shown to be highly relevant in the proliferation and survival of the cell (Figure 7)[115 118]. EGFR members of the ErbB receptor family and their effectors have been found to be mutated in various cancers, including colorectal cancer[119].

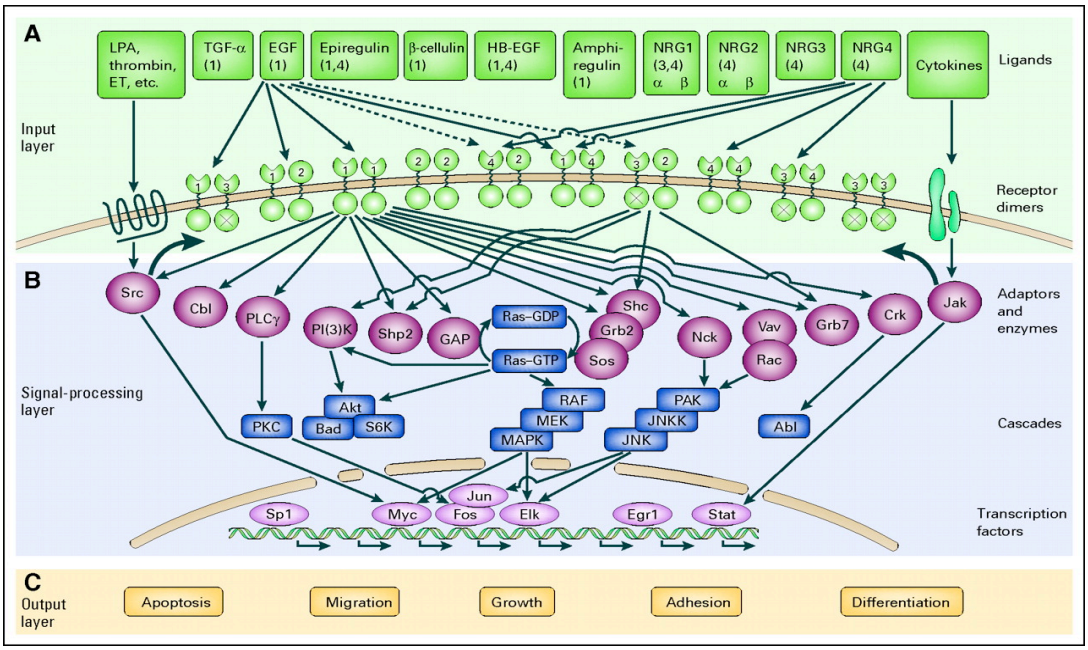


Figure 7. Network of interactions of EGFR with downstream signalling pathways in colorectal cancer. *Adapted from Harari et al, J Clin Oncol, 2007.*

3.3.2. Monoclonal antibody therapy in metastatic colorectal cancer

In order to target the molecular and cellular effects of the altered EGFR signalling, monoclonal antibodies have been developed to compete with the binding of ligands to the extracellular domain of the receptor[120]. In Switzerland, two monoclonal antibodies have been approved for treating advanced colorectal cancer in KRAS wild-type patients: Cetuximab (Erbitux®, Merck AG, Zug, Switzerland) a mouse-human chimeric anti-EGFR antibody and panitumumab (Vectibix®, Amgen Europe B.V., Netherlands) a fully human monoclonal antibody. Cetuximab has demonstrated clinical efficacy both in monotherapy and in combination with irinotecan[121 122]. Panitumumab has shown clinical benefit in terms of progression-free and overall survival when used as single agent[123 124]. Given that the advantage of those agents are largely limited to KRAS wild-type patients, the labels have been amended to cover this restriction[125 126].

3.3.3. KRAS mutation

The KRAS gene encodes for a 21kDa small G-protein[127]. About 40% of colorectal cancer patients reveal a KRAS mutation[128-130]. Generally, these mutations derive from somatic point-mutations. In more than 95% of colorectal cancer cells, KRAS mutations are mainly found in codons 12 and 13 of the KRAS-oncogene which cause the constitutive activation of the protein (Figure 8)[131-134]. Mutations in codon 61 are seen less frequently (about 3%)[135]. Further research is needed to assess whether additional codon mutations are involved in the process. Patients harbouring KRAS mutations in codon 12 or 13 have shown resistance to treatment with EGFR monoclonal antibodies like cetuximab[129 136-138]. In addition to the predictive value, KRAS mutation is discussed as a prognostic marker in terms of metastatic potential, prognosis, progression-free and overall survival[139 140].

3.3.4. BRAF mutation

Recent clinical data suggests that KRAS wild-type patients harbouring BRAF mutation do not benefit from anti-EGFR therapy[133 141]. In colorectal cancers, BRAF mutations are found in about 8% to 10% of KRAS wild-type cells[142 143]. Hence, KRAS and BRAF mutations occur in a mutual exclusive manner[141]. The most common BRAF mutation is the V600E (substitution of glutamic acid for valine at position 600) which leads to constitutive activation of BRAF independent of KRAS signalling (Figure 8)[134 144]. Furthermore, BRAF-V600E mutation is linked to microsatellite instability (MSI)[145]. Similar to KRAS, there is evidence that BRAF may also be used as a prognostic marker[146].

3.3.5. Testing for KRAS/BRAF mutation

According to the provisional clinical opinion of the ASCO, monoclonal antibody therapies directed against EGFR are not indicated if tumour cells of advanced colorectal cancer patients are a carrier of a KRAS mutation[147]. Hence, the genetic mutation analysis for KRAS is mandatory before the treatment with cetuximab or panitumumab. For an accurate KRAS testing procedure, the European Society of Pathology in collaboration with the European Quality Assurance Council and the ASCO have established guideline recommendations[116 147]. Nevertheless, until now, there is no official KRAS testing method and international guidelines for assessing predictive markers are still in process[116]. Testing for BRAF mutation has recently been introduced in some laboratories.

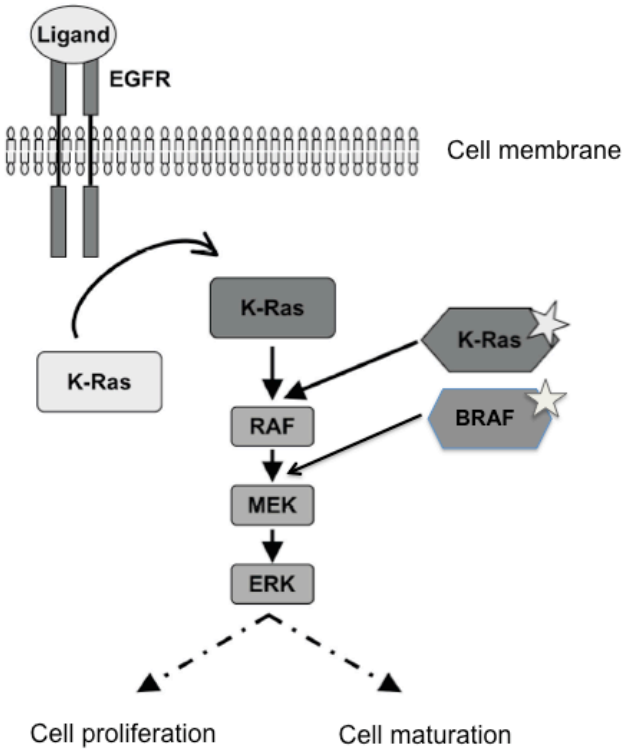


Figure 8. KRAS and BRAF signal transduction. Ligand-binding (e.g. EGF) leads to dimerisation of EGFR-protein and hence to the activation of the cytoplasmatic signalling cascade (KRAS-BRAF-MEK-ERK) which stimulates cell-proliferation and cell–maturation. By a mutation in the KRAS or BRAF-gene sequence, KRAS or BRAF (asterix) get oncogenic and induce the signalling cascade independent of EGFR. This results in strongly enhanced proliferation and maturation of the tumour cell. *Adapted from Bode et al. UZL-News: Ausgabe Nr. 18 (2008).*

There are several methods available to detect KRAS and BRAF mutations in solid tumours like, e.g., direct DNA sequencing allele-specific real-time polymerase chain reaction (PCR), analysis of high-resolution melting curve, pyrosequencing or others[57 134 148-151]. FFPE biological samples serve as material for the gene status assessment. Most assays identify point mutations in tumour samples, nevertheless, not all techniques are able to detect rare mutations. The results of the mutation analyses are mainly influenced by the tumour purity, fixation and the procedure of the DNA extraction, the selection the protocol of the mutation analyses and finally, the reporting of the results[127 152]. Few studies have determined the pros and cons of different assays, but test results were similar for most[153-155]. Basically, the selection of the test approach is laboratory dependent.

Sanger method

The traditional cycle sequencing reaction on the basis of the Sanger method searches for KRAS point mutations in codons 12 and 13[156]. This method is the “gold standard” for KRAS mutation analysis, also in Swiss laboratories (Figure 9)[157 134 158]. The main features of this approach are the potential to define the specific point-mutation and the capacity to identify all possible base substitutions, small insertions or deletions[154]. These assays feature high sensitivity and perfect specificity, hence false negative or false positive results are scarce, but cannot be ruled out entirely. The exact sequence and the performance of the test by the laboratory primarily determine the test results[154].

Allele-specific PCR

The assay for an allele-specific PCR requires sequence-specific probes and assesses targeted mutations in codons 12 and 13. Hence, only those mutations included in the assay can be identified. Due to the selective DNA amplification of mutated alleles only, the PCR based approach is characterised with a high test-sensitivity[57 153]. This method has been applied in several pivotal studies[124 136 159].

Pyrosequencing

Pyrosequencing is a bioluminescence procedure[154]. Individual bases or short stretches of DNA sequences are identified by this technique. Clustered mutations are determined with high sensitivity[150]. In addition to this, there is a possibility to execute separate assays on the same run[160].

High-resolution melt curve analysis

Quantitative PCR with melting curves takes advantage of different melting temperatures due to genetic alterations. Given that mutated sequences have less affinity for the wild-type DNA probe, they detach at a lower temperature than perfectly matched wild-type sequences. Fluorescent probes are used to detect disparities in the melting curve. False positive cases can be found in about 5% and additional sequence analyses are needed for confirming mutant samples[154 153].

Restriction fragment length polymorphism

Compared to wild-types, KRAS/BRAF mutations cause a variation in cut sites by restriction enzymes. The restriction fragment length polymorphism is highly sensitive, but requires additional sequence analyses in mutation-positive cases[153].

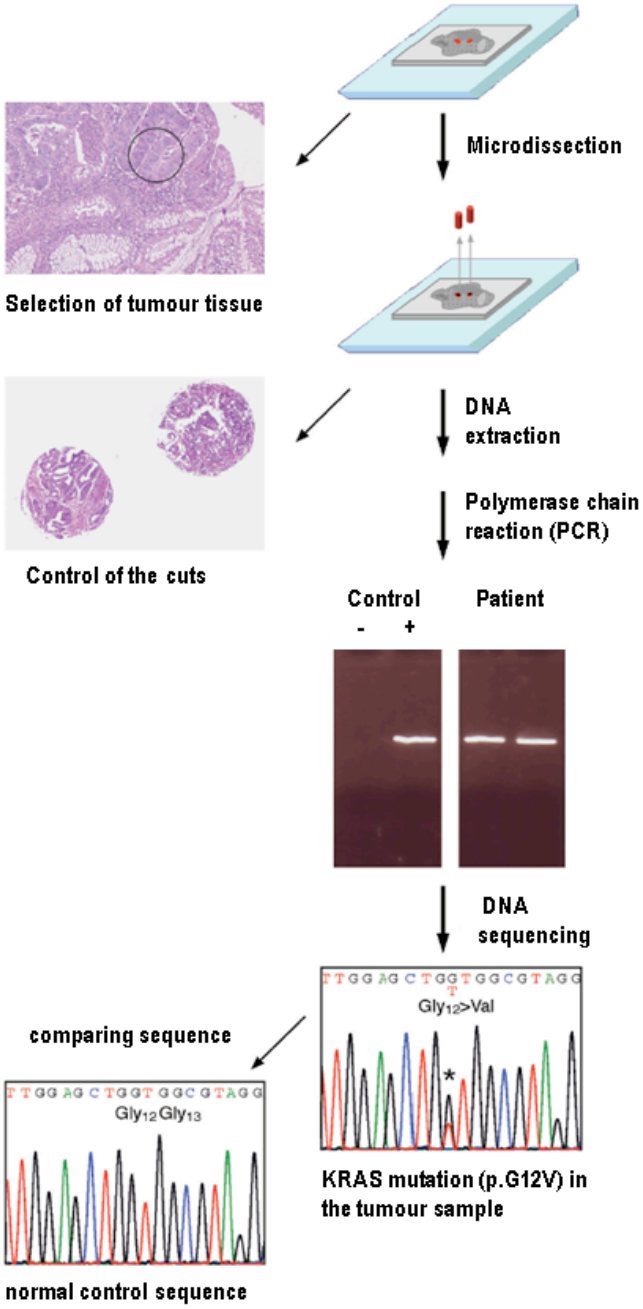


Figure 9. KRAS mutation analysis by Sanger. After DNA extraction of isolated tumour samples (tumour cell fraction over 50%), PCR amplification specific for KRAS is carried out. Afterwards, the amplification-products are sequenced. Mutations are identified by comparisons with the normal sequence. *Adapted from Bode et al. UZL-News: Ausgabe Nr. 18 (2008).*

Part IV - Results

1. Human epidermal growth factor receptor 2 expression in early breast cancer patients: a Swiss cost–effectiveness analysis of different predictive assay strategies

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This study represents the major part of my PhD. I started with this project at the beginning of my PhD. All ideas, the Markov model, the manuscript content and structure were developed and defined by me and my direct and indirect supervisors Prof. Dr. med. Thomas D. Szucs, Prof. Dr. med. Holger Moch and PD Dr. Matthias Schwenkglenks.

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Human epidermal growth factor receptor 2 expression in early breast cancer patients: a Swiss cost–effectiveness analysis of different predictive assay strategies

Patricia R. Blank · Matthias Schwenkglenks · Holger Moch · Thomas D. Szucs

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Abstract Trastuzumab has conferred significant clinical benefits in HER-2-positive breast carcinomas. HER-2 status is determined by immunohistochemistry (IHC) and/or fluorescence in situ hybridisation (FISH), but appropriate assessment of HER2 status remains subject to considerable debate. Data on the health economic impact of HER-2 test strategies are limited. A life-long Markov state transition model was used to assess costs and effectiveness of HER-2 assay strategies (based on IHC, FISH, both combined or FISH confirmation of IHC2+) for a hypothetical cohort of early breast cancer patients from the perspective of the Swiss health system. We compared clinically relevant strategies of predictive testing and subsequent trastuzumab treatment of HER-2-positive patients only. FISH testing was the most cost–effective strategy with an incremental cost–effectiveness ratio of €12,245 per additional quality-adjusted life-year (QALY) gained, compared to no trastuzumab treatment. The next best strategy was parallel IHC and FISH, with costs of €400,154/QALY gained compared to FISH alone. FISH as primary HER-2 testing modality remained the preferred option in deterministic and probabilistic sensitivity analysis. Predictive testing to identify adjuvant breast cancer patients who benefit from trastuzumab treatment is a clinical and economic necessity. Our model identifies FISH as the most cost–effective approach.

Keywords Cost–effectiveness · Adjuvant · Breast cancer · Predictive tests · Trastuzumab

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Introduction

Human epidermal growth factor receptor 2 (HER-2/neu, hereafter referred to as HER-2), is a transmembrane receptor tyrosine kinase expressed in epithelial cells including the breast. Approximately 20–25% of breast cancers patients show HER-2 protein overexpression and/or HER-2 oncogene amplification [1–4]. Both are markers for aggressive disease [5, 6] and the molecular targets of trastuzumab (Herceptin®, Roche Pharma, Switzerland) and lapatinib (GlaxoSmithKline, London, UK). Trastuzumab, a humanized monoclonal antibody, is used successfully in the therapy of HER-2-positive invasive breast carcinomas [7–10]. In the adjuvant setting, it substantially reduces recurrence rates and overall mortality in combination with chemotherapy [11–14]. There is now consensus on a life-prolonging effect in metastatic, early node-positive and node-negative HER-2 positive invasive breast cancers. Trastuzumab has also dramatically increased treatment costs [15].

Gene amplification and protein overexpression can be identified by immunohistochemistry (IHC) or fluorescence in situ hybridisation (FISH), respectively [7]. Despite a long history of predictive HER-2 testing in breast cancer

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patients, there is still no consensus on the most appropriate testing approach. Selection criteria include accuracy, reproducibility and precision but also cost [16]. Published results comparing HER-2 status determined by FISH or IHC in formalin fixed, paraffin embedded (FFPE) tissues are contradictory. Standardization of IHC in FFPE tissue samples is difficult due to pre-analytical problems and high subjectivity in interpretation. Concordance rates range between 80 and 90%, depending on the methodology, instrumentation and experience of the laboratories carrying out the tests [17]. This implies significant numbers of false negative test results, which may have dramatic consequences for the affected patients [18]. Current American Society of Clinical Oncology and the College of American Pathologists (ASCO-CAP) guidelines recommend the use of IHC for initial evaluation of HER-2 status but initial use of FISH is also discussed [19]. Arguments for FISH include better reproducibility and accuracy, although FISH is more expensive than IHC [20].

Expensive new cancer therapies are usually regarded as appropriate if trial data show clinically relevant improvements [21, 22]. Several publications have addressed the cost–effectiveness of trastuzumab in HER-2-positive breast cancer patients [23–25]. Markov models have been used to evaluate the cost–effectiveness of HER-2 testing strategies in the adjuvant and metastatic settings [26–28] but comprehensive cost–effectiveness analysis comparing alternative assay strategies are limited.

Using a life-long Markov state transition model, we evaluated the health economic impact of trastuzumab treatment of adjuvant breast cancer in Switzerland and the influence of different HER-2-testing strategies (IHC, FISH, both combined or FISH confirmation of IHC2+ status) [29]. The model can also be used for similar decision problems arising with other predictive tests in pathology.

Methodology

Overview of breast cancer disease model

A Markov model with a cycle length of 1 year was used to reproduce the disease process and economic consequences. Economic endpoints were the costs associated with each strategy. Effectiveness was assessed as quality-adjusted life-years (QALYs). Incremental cost–effectiveness ratios (ICERs) were planned to be calculated if applicable, i.e. in non-dominant situations. The time horizon of the analysis was life-long (50 years).

Costs were assessed from the perspective of the Swiss health care system. Consequently, non-medical and indirect costs were disregarded. Direct medical costs included drug costs, costs for predictive testing (where applicable), gynaecological examinations, diagnostic procedures and hospitalization (Table 3). Costs and effects were discounted at 3% [21]. Costs are shown in Euros (€). In March 2009, €1.00 equalled Swiss Francs (CHF) 1.50.

Patient populations studied

The model assessed a hypothetical cohort of female breast cancer patients aged 50 years, of whom 20% were HER-2-positive. The HER-2-positive patient population was defined by the eligibility criteria of the HERA trial [12]. In brief, patients had centrally validated HER-2-positive early stage invasive breast cancer with either node-positive or node-negative disease status (disease-free status). They completed local regional therapy and at least four courses of predefined standard adjuvant or neoadjuvant chemotherapy. Eligibility criteria for disease-free HER-2-negative patients were WHO performance status 0–1 with a confirmed HER-2-negative status. They had undergone breast surgery with axillary-node dissection or sentinel-node biopsy for invasive breast carcinoma [11].

Strategies compared

We assessed the following testing strategies: IHC alone, FISH alone, parallel IHC and FISH, sequential testing with FISH confirmation of IHC2+. Patients with positive IHC (2+ or 3+) and/or positive FISH received adjuvant trastuzumab treatment. Patients with no or a very low HER-2 expression levels (IHC 0 or 1+ or negative FISH) received standard treatment. Costs and effects of no trastuzumab treatment and a strategy of trastuzumab treatment of all patients with no predictive testing were used as reference values. The latter does not represent a clinically relevant option but was added to demonstrate the overall magnitude of the benefits achieved with predictive testing.

False positive and false negative test results lead to inadequate treatment of the affected patients. Sensitivity and specificity of IHC and FISH was assessed from published literature [30]. Sensitivity and specificity of the parallel testing strategy were calculated according to the "believe-the-positive" approach, i.e. the combined result was positive if one test indicated a positive result. Both tests were regarded as conditional independent (Table 1) [31].

Disease stages

The simulated population moved through distinct disease states, namely, disease-free survival, local recurrence, regional recurrence, metastatic disease and death (Fig. 1).

Table 1 Testing strategies and test characteristics

	Test strategy	Test	Cut-off for HER-2 positivity	Sensitivity (±95% CI)	Specificity (±95% CI)	Ref.
1.	All	IHC	2+ and 3+	0.91 (0.88–0.94)	0.75 (0.72–0.77)	[30]
2.	All	FISH	≥2.0[b]	0.98 (0.87–1.0)	0.9 (0.82–0.95)	[30]
3.	All, parallel testing[a]	IHC	2+ and 3+	0.9982 (0.9844–1.0)	0.675 (0.5904–0.7515)	[30, 31]
		FISH[a]	≥2.0[b]			
4.	First all	IHC	3+	0.905 (0.893–0.933)	0.987 (0.976–0.992)	[17]
	Second: If IHC2+	FISH	≥2.0[b]			
5.	No test, all trastuzumab					
6.	No test, no trastuzumab[c]					

NB: sensitivity and specificity of the combined tests remain in sequential or parallel testing order the same [58]

[a] *BTP* belief the positive. 1 positive test is enough for + results. Negative result if both test −

[b] Ratio HER-2/CEP17 signal

[c] Reference strategy

Local recurrence was defined according to the American Joint Committee on Cancer (AJCC) as isolated ipsilateral in-breast cancer recurrence after breast-conserving therapy of a stage 0–III breast carcinoma [32]. Regional recurrence included patients with cancer recurrence in the axilla with or without in-breast recurrence after breast-conserving therapy of stage 0–II breast carcinoma [33]. Metastatic disease implied women with progressive metastatic breast cancer without previous chemotherapy treatment for metastatic disease [7].

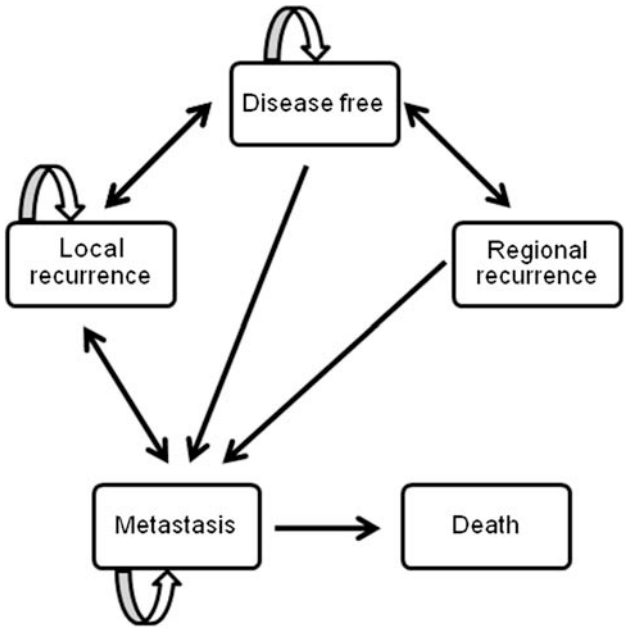

Fig. 1 Markov model starting with the disease-free health state. Diagram of model structure, comprising five health states: disease free, local recurrence, regional recurrence, metastasis (distant recurrence) and death

Clinical data sources

Clinical model inputs, namely, state transition probabilities for patients with HER-2-positive and HER-2-negative breast carcinomas (Table 2), were derived from the literature. We disregarded phase II trials, studies only presented as conference abstracts, studies with very low sample size, and studies with insufficient information for being used in our model. Efficacy results from studies of monoclonal antibodies targeted against HER-2 other than trastuzumab were not taken into account. Modelling of disease-free survival was based on HERA [12]. We assumed that HER-2-positive individuals with trastuzumab treatment would have the same transition probabilities as the patients receiving adjuvant trastuzumab in HERA. The recurrence rates seen in the HERA comparator group were applied to our HER-2-positive group without trastuzumab treatment. In the HER-2-negative situation, transition probabilities were assumed to be unaffected by trastuzumab treatment [11].

The future history of patients entering the local and regional recurrence states was derived from published retrospective reviews of medical records and was not dependent on HER-2 status [34, 35]. One-year survival rates in metastatic breast cancer patients stemmed from two phase III trials of standard treatment plus trastuzumab versus best supportive care [7, 36]. It was assumed that after 5 years, the risk of reappearing metastasis would decline by 10% annually [37].

Overall mortality rates of the Swiss female population was taken from published Swiss life tables [38].

Utilities

Utilities were based on a study using the self-administered EQ-5D questionnaire [39]. Responses were combined with

Table 2 Annual transition probabilities

HER-2 status Trastuzumab		+ Yes	+ No	− Yes	− No	Ref.
Disease state	Transition to					
Disease free	Disease free	0.934	0.879	0.975	0.975	[11, 12, 59]
	Local recurrence	0.01	0.022	0.004	0.004	
	Regional recurrence	0.006	0.008	0.004	0.004	
	Metastatic disease[a]	0.05	0.091	0.017	0.017	
Local recurrence	Disease free	0.878	0.878	0.878	0.878	[35]
	Local recurrence	0.028	0.028	0.028	0.028	
	Metastatic disease[a]	0.094	0.094	0.094	0.094	
Regional recurrence	Disease free	0.895	0.895	0.895	0.895	[34]
	Metastatic disease[a]	0.105	0.105	0.105	0.105	
Metastatic disease	Metastatic disease[a]	0.78	0.67	0.788	0.788	[7, 36]
	Death	0.22	0.33	0.212	0.212	

[a] Transition probabilities only shown for first 5 years. In the subsequent cycles, the model assumed a declined recurrence rate of 10% after each cycle

visual analogue scale-based population preference values. Utilities per disease stage were: first year after primary breast cancer, 0.696 (95% confidence interval (CI) 0.634–0.725); first year after recurrence, 0.779 (CI 0.700–0.849); second and subsequent years after primary breast cancer/recurrence, 0.779 (CI 0.745–0.811); metastatic disease state, 0.685 (CI 0.620–0.735) [39].

Medical resource use

HER-2-positive group

Disease-free status

HER-2-positive patients received trastuzumab after excision of early stage breast cancer and completion of chemotherapy. Trastuzumab dosing and planned treatment duration corresponded to the regimen used in HERA, with a 8 mg/kg loading dose and 6 mg/kg dose every 3 weeks during 1 year [12]. We assumed that 15% of the patients would receive an additional 150 mg vial due to higher weight (>74 kg). Echocardiography was performed quarterly during trastuzumab treatment [12]. All patients received gynaecological examinations [40]. During 5 years, half of HER-2-positive patients were treated with aromatase inhibitors (letrozol 2.5 mg/day or anastrozol 1 mg/day) [12].

Local and regional recurrence

Mammography, gynaecological examinations, diagnostic ultrasound, radiotherapy and surgery including hospitalization, and aromatase inhibitors (as described above) were used in these patients [25]. Local recurrence was assumed to be localized in the thoracic wall (40%) or in the breast (60%) [41].

Metastatic state

Chemotherapy, radiotherapy, diagnostic ultrasound and palliative surgery including hospitalization, and aromatase inhibitors (as described above) were used in these patients [25]. We assumed that 80% of the patients responded to trastuzumab treatment in the first-line therapy and that half of these patients were re-treated with trastuzumab for an additional year when metastases were diagnosed [7].

Untested group

Untested patients all received trastuzumab treatment as described for the HER-2-positive group. Aromatase inhibitor was given to 70% of these patients for 5 years [12, 42, 43].

HER-2-negative group

Patients with no HER-2 overexpression did not receive trastuzumab but were otherwise treated as described for the HER-2-positive group. During 5 years, 70% were assumed to receive hormone therapy [42, 43].

Unit costs

Unit costs (Table 3) for laboratory and diagnostic interventions were derived from the official Swiss tariff list [44]. Hospital case-based flat rates and day rates were

based on Swiss Diagnosis Related Groups (DRGs) [45]. Length of hospital stay was based on data provided by the Swiss Federal Statistic Office [46]. Drug costs based on official Swiss pharmacy prices [47]. Costs of diagnostics and therapeutic interventions in each state were assessed on this basis. However, as the adjuvant therapy was assumed to be the same for all patients, costs of initial treatment (primary breast surgery and adjuvant chemotherapy) were not included.

Sensitivity analysis

Deterministic sensitivity analysis tested the precision and robustness of the results. Parameters with a direct impact on incremental costs were varied by ±30% (price of trastuzumab, price of predictive tests, costs of local and regional recurrence and metastatic disease). Medical resource use was not varied separately as it was assumed that any related uncertainty would be covered by the variation of unit costs. The discount rate was set to 0 and 6%.

In addition, variables subject to statistical uncertainty (sensitivity and specificity of IHC and FISH, metastatic, local and regional recurrence rates, utilities) were varied within their 95% confidence intervals (CIs) [48]. The prevalence of a normal (negative) HER-2 expression pattern was varied between 75 and 85%.

Probabilistic sensitivity analysis

Uncertainty around the base case results was additionally assessed by probabilistic sensitivity analysis (PSA), using 10,000 sets of parameter values randomly sampled from beta distributions reflecting the ranges of variation used in deterministic sensitivity analysis [49]. Parameters covered included HER-2 prevalence, utilities, transition probabilities, and test sensitivity and specificity. Unit costs were not subject to uncertainty and therefore not included in the PSA [44].

Model implementation

The Markov model was implemented in TreeAge Pro® 2009 (TreeAge Software Inc, Williamstown, MA, USA).

Table 3 Cost per type of resource use (per first year in € per patient)

Type of resource	Duration/amount	Unit cost (€)	Ref.
Hormonal therapy	1 year	2,233	[44, 47]
Trastuzumab price (Herceptin®, Roche, Switzerland)	1 vial per 150 mg	860	[47]
	1 vial per 440 mg	2,341	
Trastuzumab treatment (Incl. Infusion and 4× echocardiography)	1 year	42,588	[44, 47]
IHC test	1 test	53	[44]
FISH test[a]	2 test probes	686	[44]
Gynaecological examination[b]	1	142	[44]
Mammography	1	107	[44]
Sonography	1 year	100	[44]
Surgery	1 year	1,275[c]	[44]
		2,778[d]	
Material	1 year	167	[44]
Anaesthesia	1 year	540	[44]
Radiotherapy	1 year	4,688[e]	[44]
		8,467[f]	
Hospitalization	7.6 days	2,281[g]	[60]

[a] Based on the resource use in Swiss laboratories

[b] According to the Swiss Consortium for Gynaecological Oncology and Obstetrics (AGO) [40]: four examinations per year in the years 1–3, two examinations in the years 4–5, one examination in the years 5–10 and biennial examinations thereafter

[c] Local recurrence in the breast

[d] Thoracic local recurrence and regional recurrence

[e] For thoracic local recurrence

[f] For regional recurrence

[g] Average duration of stay of C500 to C509 (ICD10 classification) during 2005 in Switzerland

Results

Base case analysis

Effect

Differences in effectiveness between the strategies involving trastuzumab treatment arose from imperfect sensitivity and specificity of the testing strategies (Table 1). Some HER-2-positive patients had false negative test results and hence did not receive trastuzumab, which lead to a loss of QALYs. Therefore, the no testing strategy (where all patients received trastuzumab) accrued most QALYs (12.751 QALYs per patient). The testing strategies accrued between 12.741 and 12.750 QALYs. At the lower end, the no trastuzumab strategy resulted in 12.254 QALYs (Table 4).

Costs

Trastuzumab substantially increased costs in both the testing and non-testing strategies, compared to no trastuzumab treatment. However, the increase was distinctly lower in the testing strategies. Here, trastuzumab costs were strongly reduced as therapy was targeted to those patients who profited most (Table 4).

Per-patient total lifetime costs in the predictive testing strategies ranged from €38,153 (FISH confirmation of IHC2+) to €41,830 (parallel IHC and FISH). FISH confirmation of IHC2+ saved €62 in comparison to FISH alone. If FISH alone was used, per-patient savings compared to IHC alone and parallel IHC and FISH would be €1,736 and €3,615, respectively.

Incremental cost–effectiveness

The reference (no trastuzumab) strategy was least costly and least effective (€32,258 and 12.254 QALYs per patient) (Table 4). FISH alone testing was associated with a per-patient cost of €38,215 and resulted in 12.741 QALYs, corresponding to an ICER of €12,245/QALY when compared with the no trastuzumab strategy. This was the most favourable ICER observed. FISH alone testing dominated IHC alone and FISH confirmation of IHC2+. In the latter comparison, FISH alone was in a situation of extended dominance [50], e.g.it was slightly more expensive but showed a better incremental cost–effectiveness ratio than the comparator. Superior characteristics of the FISH test lead to a gain in clinical effectiveness and hence, clinical savings that over-compensated or near-compensated much higher test costs. The ICER of parallel IHC and FISH was €400,154/QALY compared to FISH alone. ICERs for the non-testing approach were prohibitively high. Figure 2 summarizes cost–effectiveness results.

Current Swiss data show an annual average of 5,091 incident breast cancer cases between 2001 and 2005 [51]. On this basis, FISH confirmation of IHC2+ versus FISH alone would lead to cost savings of €315,642, and lose 245 QALYs, per year. FISH alone compared to IHC alone would save €8,837,976, and gain 177 QALYs, per year. FISH alone compared to parallel IHC and FISH would lead to savings of €18,403,965 and a loss of 46 QALYs.

Table 4 Base case cost–effectiveness analysis (CEA) of different testing strategies (reference: no trastuzumab)

Test strategy	Lifetime cost per person	Lifetime efficacy	*C/E*	Incremental costs[a]	Incremental efficacy[b]	ICER
Unit	€	QALY	€/QALY	€	QALY	€/QALY
No trastuzumab[c]	32,258	12.254	2,632	–	–	–
IHC first (FISH only for IHC2+)	38,153	12.693	3,006	(5,895)[d]	(0.4384)[d]	Dominated[d]
FISH alone	38,215	12.741	2,999	5,957[e]	0.4865[e]	12,245[e]
IHC alone	39,951	12.706	3,144	(1,736)[f]	(−0.0348)[f]	Dominated[f]
Parallel IHC and FISH	41,830	12.750	3,281	3,615[g]	0.0090[g]	400,154[g]
NO test	53,860	12.751	4,224	12,030[h]	0.0009[h]	13,456,577[h]

[a] Relative to the strategy with the next lower cost

[b] Relative to the strategy with the next lower efficacy

[c] Reference strategy

[d] Compared to the reference strategy (no trastuzumab)

[e] Extendedly dominated by FISH alone (extended dominance: is applied to remove from consideration strategies whose cost–effectiveness is inferior in comparison with at least one more expensive strategy)

[f] Dominated by FISH alone (simple dominance: a strategy is dominated by another if the former both costs more and is less effective)

[g] Compared to FISH alone

[h] Compared to parallel IHC and FISH

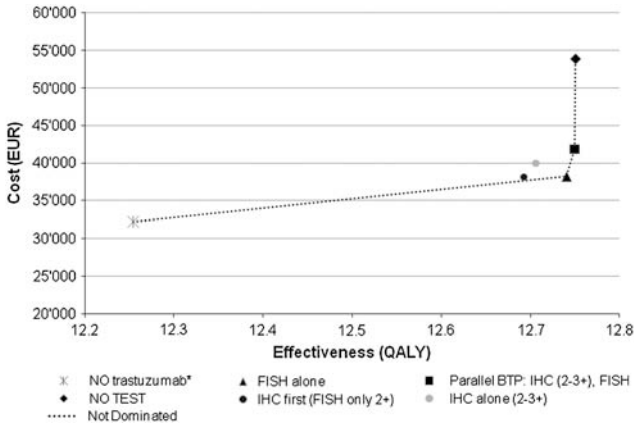

Fig. 2 Cost–effectiveness analysis. Graphical representation of incremental cost–effectiveness results. IHC alone (2–3+) is dominated by FISH alone, i.e. less effective and more expensive. IHC first (FISH only 2+) is extendedly dominated by FISH alone, i.e. less expensive but also less cost–effective. For the remaining strategies, the slope of the *dotted line* represents incremental cost–effectiveness

Sensitivity analysis

In deterministic sensitivity analysis, varying the price of trastuzumab and the discount rate had substantial influence on the results. Variation of other unit costs (apart from trastuzumab), cancer recurrence rates, test sensitivity or specificity, utilities or the HER-2 overexpression pattern did not influence the ranking of strategies. The ICERs for the non-dominated strategies were essentially sustained in all situations analyzed (Fig. 3, Table 5). The rank order of the testing strategies was also robust (Table 5). However, if the specificity of FISH alone was set a low value of 0.82 (while specificity was left unchanged for the other strategies), FISH confirmation of IHC2+ would become the preferred strategy due to its much higher specificity value. None of the other analyses performed affected the preferability of FISH alone (Fig. 3).

At a willingness to pay per QALY gained of €13,333, the FISH testing approach became dominant until at €380,000, parallel FISH and IHC became the preferred strategy (Fig. 4a). Further PSA results are shown in Fig. 4b.

Discussion

We modelled the cost–effectiveness of different predictive HER-2 testing strategies, prior to trastuzumab treatment of adjuvant breast cancer patients, from a Swiss health system perspective. FISH alone testing with subsequent trastuzumab treatment of HER-2-positive patients was identified as the most cost–effective approach, with an ICER of €12,245 per QALY gained compared to no trastuzumab use. It dominated other testing strategies or these showed unfavourable cost–effectiveness ratios. Sensitivity analysis showed these results to be robust over a wide range of assumptions. As a limitation, we did not take into account a possible

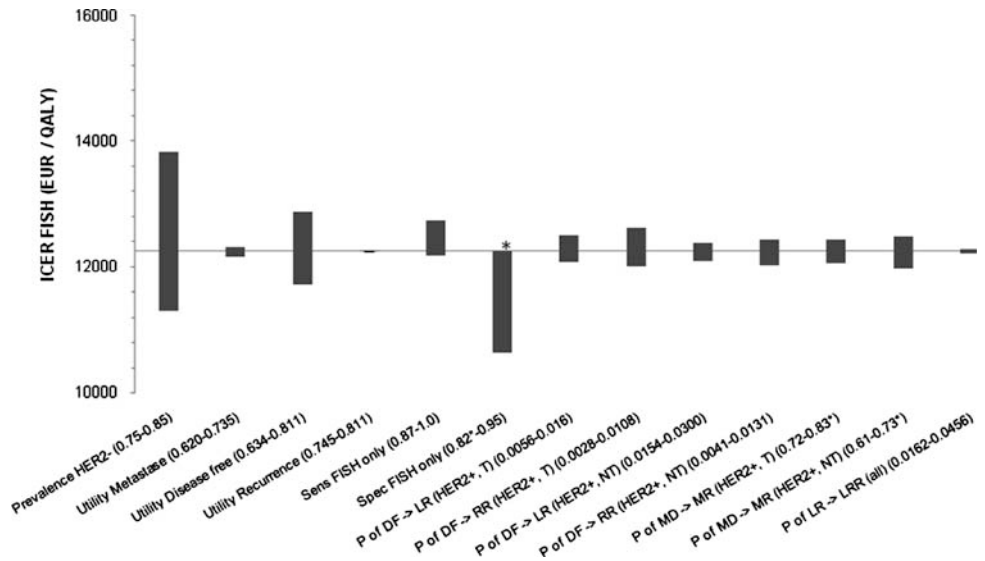

Fig. 3 Plot of the deterministic sensitivity analyses for parameter uncertainty with regard to the ICER of FISH testing compared with no trastuzumab. *Larger bars* indicate stronger sensitivity of the base case ICER of FISH testing versus the reference strategy to uncertainty around the respective parameters. *DF* disease free, *FISH* fluorescence in situ hybridisation, *ICER* incremental cost–effectiveness ratio, *IHC* immunhistochemistry, *LLR* local/regional recurrence, *LR* local recurrence, *MD* metastatic disease, *MR* metastatic recurrence, *NT* no trastuzumab, *P* probability, *RR* regional recurrence, *Sens* sensitivity, *Spec* specificity, *T* trastuzumab. *In this sensitivity analysis, FISH confirmation of IHC2+ becomes the preferred strategy with an ICER of €13,448 compared to reference strategy

Table 5 One-way sensitivity analysis of incremental costs (€) per QALY gained (ICER) without dominated strategies

Testing strategy	FISH alone vs. no trastuzumab	Parallel testing[c] vs. FISH alone	NO TEST vs. parallel testing
Baseline	12,245	400,154	13,456,577
Price trastuzumab +30%	15,982	531,788	17,377,558
Price trastuzumab −30%	8,507	268,544	9,549,342
Price all predictive tests +30%	12,398	398,547	13,396,396
Price all predictive tests −30%	12,091	401,785	13,530,503
Cost of FISH test probe −50%	11,892	400,129	13,655,867
Cost metastatic basis treatment +30%[a,b]	11,806	399,727	13,463,011
Cost metastatic basis treatment −30%[a,b]	12,683	400,605	13,463,889
Cost local recurrence +30%[a]	12,181	400,102	13,463,386
Cost local recurrence −30%[a]	12,308	400,230	13,463,514
Cost regional recurrence +30%[a]	12,243	400,164	13,463,448
Cost regional recurrence −30%[a]	12,246	400,168	13,463,451
Discount rate 6%	18,721	636,009	21,215,854
Discount rate 0%	7,644	230,451	7,818,473

[a] Without consideration of hormone therapy

[b] Price for trastuzumab not included

[c] Parallel both tests (BTP): either IHC (2–3+) or FISH+ test result needed for HER-2+ status

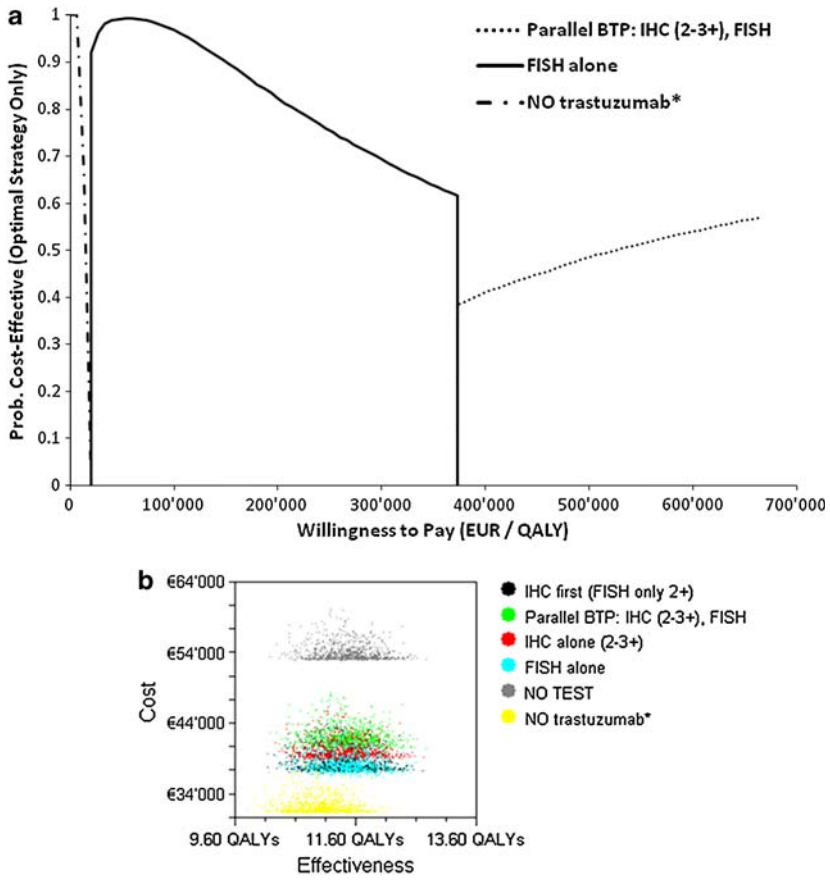

Fig. 4 Results from the probabilistic sensitivity analysis (PSA). **a** Acceptability frontier. The cost–effectiveness acceptability frontier shows the PSA-based probability of testing strategies of being cost–effective. For different willingness to pay thresholds, different strategies are optimal. For each threshold, only the probability for the optimal strategy is shown. **b** Incremental cost (€)–effectiveness scatter plot of all testing options. The cost–effectiveness scatter plot uses the cost–effectiveness plane to plot a test cost and effectiveness pair for each recalculation of the model (10,000 runs)

influence of false positive and false negative test results on the event risks reported in HERA and in the other trials used for deriving transition probabilities in this modelling study. This would have required complex correction procedures and tentative assessments indicated a minor impact.

In routine practice, many local laboratories only use IHC. Central laboratories often use FISH to confirm IHC2+, as was the case in the HERA study [12]. Both of these strategies were dominated by the FISH alone strategy in our model. The inferiority (extended domination) of FISH confirmation of IHC2+ was due to this strategy, clinical characteristics, although it was cheaper than FISH alone.

In Switzerland, many central laboratories have started to use primary FISH assays. However, IHC may be added in unclear cases. The implications were difficult to assess as no sensitivity or specificity data for FISH equivocal samples (HER-2/CEP17 ratio signal between 1.8 and 2.2) were available from the literature. A tentative assessment assuming a hypothetical sensitivity of 0.892 (CI 0.766–0.94 [30, 31]) indicated a quality-adjusted survival of 12.470 QALYs and hence no further gain in clinical effectiveness.

In a recent cost–effectiveness analysis in the metastatic setting, conducted by Elkin et al., trastuzumab treatment without predictive testing was dominated by a testing strategy not covered here, namely, the confirmation of IHC2+ or 3+ with FISH [26]. Only patients with a positive result in both tests received trastuzumab, i.e. considerably fewer than in our combined IHC and FISH strategy. It may indeed make sense to use stricter criteria for trastuzumab treatment in the metastatic than in the adjuvant setting. However, the strategy of FISH confirmation of IHC 2–3+ was also assessed for non-metastatic patients. In a meta-analysis by Dendukuri et al. [17], focusing on invasive breast cancer patients, and in a Swedish cost–effectiveness analysis studying adjuvant breast cancer patients [27], it was again identified as the strategy with the best ICER. Of note, the former study only took into account diagnostic costs; it disregarded trastuzumab costs [17]. The latter estimated IHC scores from FISH results, based on Elkin et al. [26], and thus made an implicit assumption of dependency of IHC and FISH. In a separate implementation of the model, we estimated the lifetime costs and effects of the strategy defined by Elkin et al. in the adjuvant setting. After reducing sensitivity (0.892, CI 0.766–0.94) and increasing specificity (0.975, CI 0.950–0.989) [30, 31], costs summed up to €36,706 in combination with 12.697 QALYs gained. Indeed, this would imply a favourable ICER. However, due to a low practical relevance in the adjuvant setting, and presumable lack of acceptability in a resource-rich setting, we did not incorporate this strategy into the main analysis.

Recent evidence suggests that HER-2 expression in primary and advanced tumour tissue may be discordant by 5–10% [52–57]. HER-2 status may therefore be re-assessed before starting trastuzumab treatment in metastatic breast cancer patients experiencing disease progression. However, our model focuses on adjuvant therapy and we did not attempt to assess the economic implications of this approach, as currently, this is not routine practice.

A recent review favours FISH over IHC for accuracy, reproducibility and precision reasons [16]. According to this source, 15–48% of equivocal IHC2+ breast cancers show HER-2 gene amplification. In addition, 2–8% of IHC 0/1+ breast cancers are FISH amplified. Around 5–22% of IHC 3+ breast cancers have no gene amplification (false negativity) [16]. In addition, a positive FISH status points towards a stronger responsiveness to trastuzumab. The use of FISH testing diminishes the number of patients eligible for trastuzumab therapy due to both superior sensitivity and specificity compared to IHC [16]. These findings favour primary FISH testing and are consistent with our health economic result.

Conclusion

Clinically useful predictive tests with reasonable sensitivity and specificity to predict drug-response are one cornerstone in achieving a cost–effective implementation of new treatment strategies in oncology. Currently, many novel predictive assays (e.g. *k-ras* testing in colorectal cancer, *EGFR* mutation analysis in lung cancer) are being introduced. Results from carefully conducted health economic analyses should inform future guidelines on the use of such tests. In the adjuvant breast cancer setting, primary FISH testing with subsequent trastuzumab treatment of HER-2-positive patients is a cost–effective and preferable approach.

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Conflict of interest No conflict of interest to declare.

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2. Cost Effectiveness of Cytotoxic and Targeted Therapy for Metastatic Breast Cancer: A Critical and Systematic Review

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Cost Effectiveness of Cytotoxic and Targeted Therapy for Metastatic Breast Cancer

A Critical and Systematic Review

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Contents

Abstract

Breast cancer is the leading cancer type diagnosed among women in Western countries. Despite great advances in cancer therapies, many of these patients develop non-curable metastases. The objective of cancer treatment in the metastatic setting is mainly to control symptoms and to prolong survival. The selection of the optimal chemotherapeutic regimen is affected by performance status, tumour biology, site and extent of the disease and the exposure to prior therapies. Recent developments in new kinds of cancer drugs have contributed not only to immense progress in clinical outcomes but also to dramatically increased treatment-related health costs. Cost-effectiveness analysis is a type of economic evaluation that compares costs and health outcomes of alternative intervention strategies in a systematic way.

In this review, a systematic literature search was performed and the evidence on the cost effectiveness of conventional chemotherapy and targeted therapy for metastatic breast cancer was explored.

Cost-effectiveness/-utility analysis of treatment regimens for metastatic breast cancer were identified using literature and reference searches (MEDLINE). Published reports on conventional and targeted cancer therapies were scrutinized and incremental cost-effectiveness ratios (ICERs) were abstracted. Furthermore, the quality of reporting, as well as methodological and modeling issues, were extensively discussed.

From full-text article reviews, six cost-effectiveness analyses on conventional therapies and seven studies on targeted therapies were included. Eight analyses were conducted in European countries, three in the US and two in Canada. The economic models were primarily (69%) based on clinical trial data. Results from sensitivity analyses and study perspectives were reported by all studies. Discount rates were mentioned in five articles (39%). The methods of reporting costs and effects varied considerably, as did trial design across conventional chemotherapies, which made it difficult to compare those analyses.

The pharmacoeconomic studies came to different conclusions. The actual clinical evidence does not suggest one conventional chemotherapy regimen as superior. Studies on cytotoxic agents showed mainly favourable cost-effectiveness ratios. Targeted therapies indicated both favourable and non-favourable ratios. Currently, trastuzumab is the only antibody-based targeted therapy that is established in the clinic for the metastatic setting.

Breast cancer is the most common cancer diagnosed in women in Western countries. About 25–40% of breast cancer patients develop a metastasis in the course of their illness.[1,2] Since metastatic breast cancer (MBC) is not curable, one of the main goals of treating patients is to provide palliation of symptoms and the maintenance or improvement of quality of life (QOL). The prolongation of life expectancy is a secondary goal. The armamentarium for palliative treatment contains potent endocrine treatments for the hormone receptor-positive breast cancers, bisphosphonates for the subset of patients with bone disease, targeted therapy for, so far, mainly the subgroup of HER2 (human epidermal growth factor receptor 2)-positive patients and, finally, conventional cytotoxic chemotherapy.

Conventional chemotherapeutics do not act on the diverse signalling pathways that help the tumour progress, but rather target dividing cells in general and are therefore associated with a wide range of adverse effects. For breast cancer, in particular, conventional chemotherapy for metastatic disease is usually administered after the failure of endocrine treatment. A high percentage of patients with early breast cancer receive adjuvant combination chemotherapy, which affects the choice of the regimen administered for MBC. Patients with breast cancer recurring after having received anthracyclines in the adjuvant setting usually receive a taxane-containing regimen, whereas patients who have received adjuvant taxanes usually receive an anthracycline-based regimen.[3]

Targeted drugs exploit specific molecular characteristics of the tumour and do not usually affect cells without that specific target. Several classes of antibody-based targeted therapies have raised hope in the treatment of breast cancer.[4] Trastuzumab (Herceptin®, Roche Pharma, Switzerland), a monoclonal antibody targeted to the HER2 receptor is currently routinely used in both the early breast cancer and metastatic settings for patients with HER2-positive tumours.[5] The efficacy and safety of trastuzumab as first-line treatment in MBC has been demonstrated in

several randomized controlled trials.[6-9] However, trastuzumab is limited to 15–25% of breast cancer patients overexpressing the HER2 receptor or amplifying the HER2 oncogene.[10-12] Lapatinib is an orally available dual tyrosine kinase inhibitor of the HER2 kinase and has been approved in some countries for HER2 MBC progressing under trastuzumab treatment or as first-line oral treatment in combination with endocrine therapy.[13] Pertuzumab, a further monoclonal antibody that binds a different epitope on HER2 from trastuzumab is under clinical assessment. This agent has been developed for breast cancer patients, whether overexpressing HER2 or not.[14,15] Bevacizumab (Avastin®, Roche Pharma, Switzerland) is a monoclonal antibody directed against vascular endothelial growth factor-A. Given its antiangiogenic properties, it is being evaluated in the metastatic setting, and is showing promising results.[16] Bevacizumab has been approved in a combination therapy for MBC with a negative HER2 status.[17]

The complex economics of new oncology drug developments are an important area of research.[18] However, progress in the development of new cancer treatments is connected to costs, namely treatment-related expenses and effects on QOL. Particularly expensive drugs must demonstrate relevant improvements in regard to length of life, QOL or if there is no alternative available to be regarded as justified.[19,20] In response to the growing concern about the costs of pharmaceutical products, pharmacoeconomic studies investigate the impact of new drugs or interventions on the patient's QOL and the healthcare outcome through, for example, cost-effectiveness studies. Economic analyses ideally cover clinical and economic outcomes achieved in randomized controlled trials. Such models play an important role in policy makers' decisions regarding coverage and reimbursement of products.

The aim of this review was to compare and summarize findings of published, original cost-effectiveness analyses of chemotherapy and targeted non-chemotherapy regimens for MBC that presented results as cost-per-life-year gained (LYG) or QALY. The quality of reporting was critically assessed. Particular emphasis was placed on the key drivers of cost effectiveness of the various treatment agents.

1. Literature Review

1.1 Data Source and Selection

MEDLINE and PubMed were searched systematically for all original cost-effectiveness analyses published between 2000 and 2009. Given that the field of targeted therapies is new, we included studies published only from the year 2000 onwards to ensure a comparable study population in both conventional and targeted therapeutic settings. The search included the following keywords: 'cost', 'effectiveness', 'utility', 'breast', 'cancer metastatic' and 'advanced'. A total of 671 articles were recognized in the initial literature search. Titles and abstracts were screened by two independent reviewers (KJD, PRB) to determine whether the reports were an original health economic study. The full text of studies considered important after the first screening cycle were evaluated. For literature saturation, reference lists were explored for relevant reports. Studies were included if they were reports on cost effectiveness, or cost-utility reports of MBC therapies. Descriptive cost studies, posters, editorials, publications not showing primary data or reports in languages other than English were excluded. Cost-effectiveness analyses primarily describing the health economic impact of hormonal therapies or predictive testing in targeted non-chemotherapy settings were not taken into account. Figure 1 outlines how the final sample size was reached.

Detailed information from the reports was abstracted using a pre-specified checklist. A standardized extraction form was used to gather the following issues from the studies: (i) characteristics of the study (study design, population, perspective); (ii) type and outcome of the economic analysis; and (iii) key aspects (cancer treatment and comparator strategy, clinical outcome, costs and discount rate) and parameters of the sensitivity analysis (if available). For the base-case analysis, incremental cost-effectiveness ratios (ICERs) were reported. Studies were

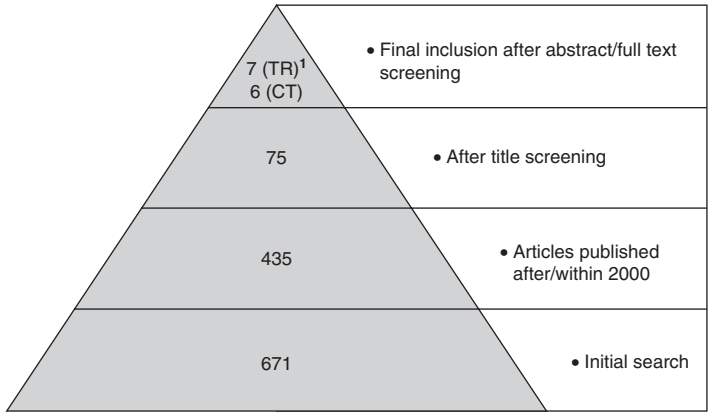

Fig. 1. Article search. **1** One article was included as a result of the reference search. **CT** = articles on conventional chemotherapies; **TR** = articles on targeted regimens.

grouped into cost-effectiveness analyses addressing either conventional chemotherapy or targeted regimens. Particular emphasis on the key drivers of cost effectiveness of the various chemotherapy and targeted regimens was given. As year of reference, the reported monetary year or the year of publication was used. Costs are shown in $US (€1 ≅ $US1.47; £1 ≅ $US1.74; $Can1 ≅ $US1).

2. Overview of Included Papers

Included studies focused on breast cancer patients in MBC. Outcome measures were given in either QALYs (7 of 13) or in LYG (6 of 13). Eight analyses were conducted in European countries (France, Greek, Norway, Switzerland, UK), three in the US and two in Canada. Only one article was published in a pharmacoeconomic and outcome research journal,[21] whereas the remaining articles were published in oncology or public health journals. The funding source was mentioned in nine studies (69%).

The methodologies used varied considerably. The studies all used model-based analyses for their calculations. Three articles[21-23] mentioned that Markov models had been established, whereas only two clearly described the methodological approach of the model. The remaining studies used other economic models. Data included were derived primarily from randomized controlled trial data (9 of 13). Two studies[24,25] were based on cancer registry and medical record information, respectively. One study[26] was conducted with data from an open, controlled, prospective study and one article[27] included data from published literature. The studies were simulated from a healthcare payer (10 of 13), a hospital (1 of 13) or a societal (2 of 13) perspective. A discount rate of 3% (3 of 13), 3.5% (1 of 13) or 5% (1 of 13) was applied. The discount rates were largely applied to both costs and outcomes. The remaining studies did not state discount rates. In the sensitivity analyses performed, mainly costs and clinical effect variables were varied. The economic analyses based on conventional chemotherapies were all considered cost effective by the authors, except one study with ixabepilone.[28] In the studies of targeted regimens, authors concluded that the monoclonal antibody treatment was cost effective (3 of 7),[25,26,29] not cost effective (3 of 7)[22,23,27] or gave no clear statement (1 of 7).[30]

The summary of cost-effectiveness results of conventional and targeted regimens is given in tables I and II, respectively.

3. Cost Effectiveness of Conventional Chemotherapies

Maniadakis et al.[32] analysed the cost effectiveness of three taxane-based regimens that are

Table I. Cost-effectiveness analyses of conventional therapies

	Dranitsaris et al.[31]	Maniadakis et al.[32]	Reed et al.[33]	Vu et al.[34]	Benedict et al.[35]	Verma and Ilersich[36]
Year of publication, country	2009, UK	2009, Greece	2009, USA	2008, Canada	2009, UK	2003, Canada
Conflict of interest	Manufacturer funded	NS	Manufacturer funded	None	Manufacturer funded; co-authorship from manufacturer	NS
Comparators	nabPac1w, nabPac3w, Doc	Pac1w, GDoc, PacCb	Ixb+Cap, Cap	Doc, Pac	Doc, Pac3w, Pac1w, nabPac3w	Cap+Doc, Doc
Line of therapy	Mostly second line (after anthracyclines)	First line (after adjuvant anthracyclines)	Second to third line (after anthracyclines and taxanes)	Second line (after anthracyclines)	Second line (after anthracyclines)	Second line (after anthracyclines)
Study design (time horizon)	RCT and basic calculations (lifetime)	RCT and basic calculations, multivariate regression (34 mo)	Stochastic decision-analytic model based on RCT (lifetime)	Retrospective population based (lifetime)	RCT and basic calculations, Markov modelling (10 y)	RCT and population based (lifetime)
Population age [y (range)]	54 (NS)	60 (27–84)	52 (25–79)	55 (26–87)	NS	NS
Perspective (outcome measure)	Third-party payer perspective (LYG)	Healthcare system (QALY)	Healthcare system (QALY)	Healthcare system (LYG)	Healthcare system (QALY)	Healthcare system (LYG)
Overall per-patient mean costs ($US)	nabPac1w 100 mg/m^2: 26 787 nabPac1w 150 mg/m^2: 47 366 nabPac3w 300 mg/m^2: 27 508 Doc: 22 486	PacCb : 30 132 GDoc: 28 434 Pac1w: 30 250	Ixb+Cap: 60 900 Cap: 30 000	Doc: 9441 Pac: 2944	Doc: 30 139 Pac3w: 23 144 Pac1w: 27 793 nabPac3w: 24 562	Cap+Doc: 13 659 Doc: 12 833

Continued next page

Table I. Contd

	Dranitsaris et al.[31]	Maniadakis et al.[32]	Reed et al.[33]	Vu et al.[34]	Benedict et al.[35]	Verma and Ilersich[36]
Incremental cost ($US)	nabPac1w 100 mg/m^2: 4301 nabPac1w 150 mg/m^2: 24 880 nabPac3w 300 mg/m^2: 5022	Pac1w vs PacCb: 118 Pac1w vs GDoc: 1816 PacCb vs GDoc: 1698	30 900	6497	Doc to Pac3w: 6995 Doc to Pac1w: 2346 Doc to nabPac3w: 5577	826
Discount rate (%)	NS	3.5	3	No	3.5	No
Outcome results (unit)	nabPac1w 100 mg/m^2: 12.8 PF mo nabPac1w 150 mg/m^2: 12.9 PF mo nabPac3w 300 mg/m^2: 11.0 PF mo Doc: 7.5 PF mo	Pac1w: 41 mo PacCb: 29.9 mo GDoc: 26.9 mo	Ixb + Cap: 1.01 y Cap: 0.84 y	Doc: 10.9 mo Pac: 8.3 mo	Doc: 1.18 y Pac3w: 0.85 y Pac1w: 0.89 y nabPac: 0.96 y	Cap + Doc: 14.5 mo Doc: 11.5 mo
Incremental effect	nabPac1w 100 mg/m^2: 5.3 mo nabPac1w 150 mg/m^2: 5.4 mo nabPac3w 300 mg/m^2: 3.5 mo	Pac1w vs PacCb: 11.1 mo Pac1w vs GDoc: 14.1 mo PacCb vs GDoc: 3 mo	32 quality-adjusted days	2.6 mo	Doc to Pac3w: 0.33 y Doc to Pac1w: 0.29 y Doc to nabPac3w: 0.22 y	3 mo
Cost-effectiveness result: ICER ($US) [base case]	nabPac1w 100 mg/m^2: 9744 per PF y nabPac1w 150 mg/m^2: 55 332 per PF y nabPac3w 300 mg/m^2: 17 226 per PF y	Pac1w vs PacCb : dominance Pac1w vs GDoc: 5286 per QALY PacCb vs GDOC: 10 969 per QALY	359 000 per QALY	30 337 per LYG	20 936 per QALY to Pac3w 7974 per QALY to Pac1w 25 568 per QALY to nabPac3w	3691 per LYG
Results of sensitivity analysis ($US)	Results robust	Results robust	Univariate sensitivity analyses/Monte Carlo simulation; threshold remained above 150 000	Univariate sensitivity analyses: 13 972–91 724	Probabilistic sensitivity analysis: ICER remains <34 800	Univariate sensitivity analyses: results robust
Authors' conclusion	nabPac is reasonable alternative to docetaxel	Pacw effective and cost-effective regimen	Ixb more expensive than other regimens	Doc more effective than Pac and may be considered cost effective	Doc is cost effective vs Pac1w, Pac3w and nabPac3w	Cap + Doc is cost effective

Cap = capecitabine; **Cb** = carboplatin; **Doc** = docetaxel; **G** = gemcitabine; **ICER** = incremental cost-effectiveness ratio; **Ixb** = ixabepilone; **LYG** = life-years gained; **nabPac** = nano-particle albumin-bound paclitaxel; **NS** = not stated; **Pac** = paclitaxel; **PF** = progression-free; **RCT** = randomized controlled trial; **1w** = once weekly; **3w** = every 3 weeks.

Table II. Cost-effectiveness analyses of targeted therapies

	Norum et al.[37]	Perez-Ellis et al.[25]	Poncet et al.[38]	Hornberger et al.[29]	Garrison and Veenstra[39]	Dedes et al.[40]	Le and Hay[41]
Year, country	2005,[a] Norway	2002,[a] France	2002,[a] France	2002,[b] UK	2009,[b] USA	2008,[a] Switzerland	2007,[a] USA
Conflict of interest	NS	NS (French MoH/French League against Cancer funded study)	NS (French MoH funded study)	NS (co-authorship from manufacturer)	NS (unrestricted grant from manufacturer)	None	None
Comparators	T+Doc, AC or Pac vs SC (Doc, AC or Pac)	T or T+Tax vs SC (Tax and/or A-based)	T+Pac vs SC (Doc or Doc+Epi)	T+Pac vs Pac	T+Pac vs Pac	Pac+Bev vs Pacw	L+C vs C
Line of therapy	First line	First line	First line	First line, second line (T only after progression)	First line	First line	Second line
Study design (time horizon)	RCT [literature] and basic calculations (lifetime)	Before-and-after design and bootstrapping method (lifetime or until date of pts' last news)	Open, controlled, prospective study and basic calculations (lifetime)	RCT and statistical matching methods/Gompertz function (5 y)	Dynamic life-cycle modelling (18 y)	Markov modelling based on RCT (lifetime)	Markov modelling based on RCT (lifetime)
Population age [mean y (range)]	T: 25–80 SC: 24–79	T: 51 (27–73) SC: 55 (26–75)	51 (30–77)	NS	Five age groups: <21, 21–29, 40–54, 55–65, >65	27–85	53
Perspective (outcome measure)	Third-party payer (LYG)	Payer perspective (LYG)	Hospital perspective [France] (LYG)	UK NHS (QALY/QALM)	Payer and social perspective (QALY)	Payer perspective (QALY)	Societal perspective (QALY)
Overall mean per-pt cost ($US) results	T: 64 968	T: 58 222 SC: 18 809	T+Pac: 48 908 SC: 16 598	T+Pac: 50 373 Pac: 18 479	T+SC: 87 728 SC: 40 000	Pac+Bev: 101 492 Pac: 42 149	L+C: 66 499 C: 46 869
Incremental cost ($US)	64 968	39 415	32 310	31 894	47 728	59 342	19 630

Continued next page

Table II. Contd

	Norum et al.[37]	Perez-Ellis et al.[25]	Poncet et al.[38]	Hornberger et al.[29]	Garrison and Veenstra[39]	Dedes et al.[40]	Le and Hay[41]
Discount rate (%)	5 (only for benefits)	NS	NS	NS	3	No	3
Treatment duration	40 wk (36 doses T)	T for max. of 1 y or until disease progression	24 wk (eight cycles) or until disease progression/death	NS	Until disease progression	Pac + Bev: 7.1 mo (followed by 3 mo Bev-monotherapy) Pac: 5.1 mo	NS
Outcome results (unit)	T: 25.8–30.5 mo SC: 21.1 mo	T: 37.02 mo SC: 18.98 mo	T + Pac: 2.4 LYG SC: 0.97 LYG	T + Pac: 12.3 QALM Pac: 6.4 QALM	T + SC: 1.26 QALY SC: 0.70 QALY	Pac + BEV: 0.90 QALY Pac: 0.69 QALY	NS
Incremental effect	3.7–8.4 mo = 0.3–0.7 LYG	18.04 mo	1.43 LYG	5.9 QALM = 0.49 QALY	0.56 QALY	0.21 QALY	0.12 QALY
Cost-effectiveness result: ICER ($US) [base case]	101 742–238 753 per LYG	40 413 per LYG	22 594 per LYG	65 250 per QALY	85 676 per QALY	278 458 per QALY	166 113 per QALY; 120 184 per LYG
Results of sensitivity analysis ($US)	Results sensitive to reduced drug cost and further improvement in survival	Cost ratio remains >11 760 per LYG and <29 400 per LYG	Threshold analysis: T flask should be 634 to achieve equivalent cost effectiveness in both groups	Monte Carlo simulation to assess distribution of cost effectiveness	Deterministic sensitivity analysis for combined indication (early and metastatic)	One-way and probabilistic sensitivity analysis: WTP of 88 200 per QALY was never reached	One-way and probabilistic sensitivity analysis (95% CLs): ICER 158 000–215 000 per QALY
Authors' conclusion	T not cost effective in MBC	Despite huge unit price, T should be considered as cost-effective treatment for MBC pts	Additional costs seem affordable and justified the use for HER2+ pts	First-line treatment with T + Pac increases OS and QALYs. This approach is cost effective	Average ICER can increase or decrease for different indications during the life-cycle of a compound	Addition of BEV is expensive given QALYs gained	Addition of L to C treatment is not clearly cost effective

a Year of monetary value.

b Year of publication.

A = anthracycline; **AC** = anthracycline + cyclophosphamide; **BEV** = bevacizumab; **C** = capecitabine; **CL** = confidence limits; **Doc** = docetaxel; **Epi** = epirubicine; **HER2+** = human epidermal growth factor receptor 2 positive; **ICER** = incremental cost-effectiveness ratio; **L** = lapatinib; **LYG** = life-year gained; **max.** = maximum; **MBC** = metastatic breast cancer; **MoH** = Ministry of Health; **NS** = not stated; **OS** = overall survival; **Pac** = paclitaxel; **Pacw** = paclitaxel weekly; **pt** = patient; **QALM** = quality-adjusted life-month; **RCT** = randomized controlled trial; **SC** = standard chemotherapy; **T** = trastuzumab; **Tax** = taxane; **WTP** = willingness to pay.

administered as first-line chemotherapy in patients with MBC who have already received anthracyclines in the adjuvant setting. This economic analysis, conducted from the perspective of the Greek national health system, was based on the randomized phase III trial[42] comparing carboplatin (area under the curve [AUC] of 6) and paclitaxel (175 mg/m^2 administered every 3 weeks for six cycles) versus paclitaxel weekly (80 mg/m^2 weekly for 12 weeks) or docetaxel 75 mg/m^2 plus gemcitabine 1000 mg/m^2 every 3 weeks.[43] The paclitaxel weekly arm appeared to be the most preferable choice among the three regimens as it prolonged overall survival (OS) more than the other combinations without being associated with higher adverse effects. The QOL was similar in all three arms. Docetaxel with gemcitabine incurred the lowest total costs per patient (€19 343; $US28 434) but proved to be less effective than the two paclitaxel-containing regimens and caused more severe myelotoxicity and mucositis. Paclitaxel with carboplatin every 3 weeks cost about the same amount per patient as paclitaxel weekly (€20 498 vs €20 578; $US30 132 vs $US30 250) but was significantly less effective. These results remained fairly constant in sensitivity analyses.

Vu et al.[34] compared the cost effectiveness of docetaxel 100 mg/m^2 versus paclitaxel 175 mg/m^2, both administered every 3 weeks. The analysis was conducted from the perspective of the Canadian healthcare system. The clinical data, in contrast to many other cost-effectiveness studies, was not based on a clinical trial but was derived from a provincial cancer registry. The OS in the docetaxel-treated group was significantly higher than among patients treated with paclitaxel (10.9 vs 8.3 months). This benefit was similar to the results of a randomized trial comparing both agents.[44] The costs per patient were substantially higher in the docetaxel group ($Can9441 vs $Can2944; $US9441 vs $US2944), which was attributed to the higher acquisition costs of docetaxel. The ICER was $Can30 337 ($US30 337) per LYG for docetaxel versus paclitaxel.

Benedict et al.[35] compared the same regimens for the UK healthcare system as Vu et al.[34] but used clinical data from a randomized controlled trial.[45,46] In contrast to Vu et al.,[34] Benedict et al.[35] included QOL data retrieved from the literature. Furthermore, the authors indirectly included two additional regimens (paclitaxel weekly and nab-paclitaxel[1] every 3 weeks) by including data from other randomized controlled trials. However, for paclitaxel weekly, evidence from two abstracts from meeting proceedings was used rather than the best available evidence.[48] In the model, the hazard ratios of docetaxel, paclitaxel weekly and nab-paclitaxel every 3 weeks were applied to the baseline hazard with paclitaxel every 3 weeks to model the progression-free and OS curves. The proportion of patients in each of the three health states (no progression, progression, death) was calculated at each time point for each treatment.

The relative difference between the mean costs per patient in the docetaxel 3-weekly group versus the paclitaxel 3-weekly group was smaller than in the population-based analysis for Canada.[34] Furthermore, the clinical benefit derived from a randomized clinical trial was higher than in the Canadian study, proving that data from randomized controlled trials are not always reproducible in clinical practice. The ICER was found to be £4583–14 694 ($US7974–25 567) per QALY for docetaxel 3-weekly compared with paclitaxel 3-weekly, weekly and nab-paclitaxel, which is regarded as acceptable for the UK healthcare system.

Verma and Ilersich[36] compared the costs and outcomes of oral daily capecitabine 2500 mg/m^2 plus 3-weekly docetaxel 75 mg/m^2 with 3-weekly docetaxel 100 mg/m^2 from the perspective of the Canadian healthcare system by combining data from a randomized controlled trial[49] with a population-based model. The randomized clinical trial showed a survival benefit of 3 months (14.5 vs 11.5 months) for the combination treatment. Combination treatment was accompanied with an increase in grade 3 adverse events (71% vs

1 Recently, a new nanoparticle albumin-bound formulation of paclitaxel (nab-paclitaxel) was developed to improve efficacy and overcome the toxicity associated with taxanes.[47]

49%), whereas the monotherapy arm showed a slightly higher rate of grade 4 events (31% vs 25%). The ICER for the combination treatment was $Can3691 ($US3691) per LYG. Unfortunately, this analysis did not account for QOL.

The efficacy and safety of nab-paclitaxel in the first- and second-line treatment of MBC were demonstrated in a large randomized trial with paclitaxel serving as the control arm. In that study, nab-paclitaxel was statistically superior to paclitaxel in terms of objective tumour (33% vs 19%; p = 0.001) and progression-free survival (PFS) [23 vs 16.9 weeks; p = 0.006].[50] There was also a trend in favour of nab-paclitaxel in OS, but it did not reach statistical significance (median 65.0 vs 55.7 weeks; p = 0.37). Patients randomized to the nab-paclitaxel arm had a lower incidence of neutropenia but higher grades of sensory neuropathy. In another trial, different dosages of nab-paclitaxel were compared with the other taxane, docetaxel. The trial compared two dosages for weekly administration (100 and 150 mg/m^2) and an every 3 week (300 mg/m^2) schedule of nab-paclitaxel versus docetaxel.[50] Nab-paclitaxel 150 mg/m^2 weekly demonstrated significantly longer PFS than docetaxel by both independent radiologist assessment (12.9 vs 7.5 months, respectively; p = 0.0065) and investigator assessment (14.6 vs 7.8 months, respectively; p = 0.012). Based on these data, which included only PFS data and no OS data, Dranitsaris et al.[31] conducted an economic evaluation from the perspective of the UK healthcare system. Nab-paclitaxel 150 mg/m^2 weekly was associated with the highest cost per patient (£27 222; $US47 366) due to the acquisition cost and costs for supportive care (growth factors, blood transfusions, antibacterials and antiemetics). The docetaxel arm was the less expensive treatment arm, with £12 923 ($US22 486) mean cost per patient. The incremental 5.4 progression-free months gained by nab-paclitaxel 150 mg/m^2 compared with docetaxel resulted in a ratio of £31 800 ($US55 332) per progression-free year gained. QOL was not considered in this cost-effectiveness analysis. The authors concluded that nab-paclitaxel can be considered a reasonable alternative to docetaxel as first-line chemotherapy for MBC and, if considering the favourable adverse effect profile of nab-paclitaxel, the inclusion of QOL and utility benefits would further improve its economic profile.

Finally, Reed et al.[33] analysed the cost effectiveness from the perspective of the US healthcare system of adding ixabepilone to capecitabine as third-line chemotherapy after progression under anthracyclines and taxanes. The results of this study should be cautiously compared with all previously mentioned cost-effectiveness analyses, as the underlying patient population had experienced recurrence or progression despite treatments with anthracyclines and taxanes, which is associated with poorer response to any chemotherapy and poorer survival expectation as such. Clinical data were extracted from a randomized controlled trial,[51,52] from which QOL results were also available and incorporated. The addition of ixabepilone prolonged OS by 32 quality-adjusted days. The incremental costs for the combination therapy amounted to around $US30 000, which resulted in an ICER of $US359 000 per QALY. The authors concluded that this ratio is higher than for other new treatments in MBC.

4. Cost Effectiveness of Targeted Therapies

Norum et al.[37] described a model-based cost-effectiveness analysis of trastuzumab in MBC patients that included data on efficacy, tolerability, gain in survival and drug costs from a third-party payer perspective. Based on data presented at breast cancer conferences[53,54] and a MEDLINE search, they assessed LYG and associated costs in patients treated with standard chemotherapy (docetaxel, anthracycline plus cyclophosphamide or paclitaxel) compared with the addition of intravenous (IV) trastuzumab 4 mg/kg (initial dose) and 2 mg/kg (weekly dose). Direct costs included drug costs, the assessment of HER2 status, and hospitalization and outpatient clinic costs. Costs for the chemotherapeutic agents were assumed to be similar between treatment arms so they were not incorporated in the model. No indirect costs were included. The incremental survival time with trastuzumab was between 0.3 and 0.7 years compared with standard

chemotherapy. Drug costs (89% of overall costs) and the prolonged treatment in the outpatient clinic (8% of overall costs) were the key factors driving costs in the trastuzumab group. Depending on survival gain and discount rate applied, incremental cost effectiveness ranged from €69 212 to €162 417 ($US101 742 to $US238 753) per LYG. Drug costs and survival time significantly influenced the base-case results in sensitivity analyses. The authors concluded that the costs of administering trastuzumab to patients with MBC for the gain of 1 year of life were considerable.

The cost-effectiveness study of trastuzumab published by Perez-Ellis et al.[25] was based on a retrospective analysis of medical files and associated cost data of HER2-positive patients treated for first metastatic progression. Trastuzumab administration was given as a single agent or in combination with chemotherapy (taxanes). Treatment with trastuzumab was limited to 1 year or until disease progression (standard schedule IV 4 mg/kg [initial dose], IV 2 mg/kg [weekly dose]). Control patients received standard treatment (taxanes- and/or anthracycline-based chemotherapy). Treatment costs were based on hospital direct costs (inpatient hospitalization stay, drug costs, imagery test, etc). Costs for predictive testing of HER2 status were omitted from the analysis. Data on QOL were not considered. In terms of OS, the trastuzumab group showed superior results (37 months vs 19 months in the non-trastuzumab group; $p < 0.001$). The per-patient costs in the trastuzumab group were considerably higher than in the non-trastuzumab group (€39 607 [$US58 222] vs €12 795 [$US18 809], respectively). The main cost drivers were the price of trastuzumab (40% of the total costs in the trastuzumab group) and the length of hospitalization (60% of total costs in the no-trastuzumab group). Of note, hospital room costs and the number of imagery tests were substantially higher in the trastuzumab group. The ICER assessed by the bootstrapping method was considered cost effective (€27 492 [$US40 413] per LYG). Bivariate sensitivity analysis was performed under several assumptions in regard to trastuzumab unit costs (−25%, −50%, −75%) and hospitalization costs (±50%). The associated ICER ranged from €8000 ($US11 760) to €20 000 ($US29 400) per LYG.

In an open, controlled, prospective study, Poncet et al.[38] evaluated the costs and effects for patients receiving a combination therapy of IV trastuzumab (3-weekly schedule of 4 mg/kg [initial dose], 2 mg/kg [maintenance dose]) and paclitaxel (trastuzumab + paclitaxel) or control therapy (any chemotherapy without trastuzumab). According to the medical files of those patients, all costs generated from the hospital were included in the analysis (overall care costs, drug costs, immunohistochemical tumour analysis, hospital stay, etc.). Effectiveness was assessed in terms of OS and PFS. The 1-year OS rate showed a significant difference between comparator and control group (0.85 vs 0.47, respectively; $p = 0.007$). The difference in 1-year PFS was not statistically significant (60% vs 42%, respectively). The mean ICER was €15 370 ($US22 594) per LYG for trastuzumab. Poncet et al.[38] concluded that the strategy of adding trastuzumab to paclitaxel therapy seems to be affordable from the perspective of the French healthcare system. To obtain equivalent mean cost effectiveness in both groups, the threshold analysis evaluated that the costs of a trastuzumab flask would need to be €432 ($US635) instead of the €626 ($US920) paid in 2002.

Hornberger et al.[29] assessed the cost effectiveness of first-line trastuzumab treatment of MBC HER2-positive patients (trastuzumab + paclitaxel vs paclitaxel). Trastuzumab was administed once weekly (4mg/kg loading dose, 2 mg/kg maintenance dose).[55] Patients with progressing cancer were allowed to receive trastuzumab as second-line treatment (75% in paclitaxel group, 47% in trastuzumab + paclitaxel group). Data on response duration and OS were derived from a randomized controlled study ($n = 469$).[7] The model comprised the costs of chemotherapy; the rate, severity and costs of adverse events; and QOL. Clinical benefits were measured in achieved prolonged survival and improved quality-adjusted life-months (QALMs). The combined therapy arm achieved a survival mean of 25.0 months compared with 15.2 months in the paclitaxel arm. In addition to this, the trastuzumab + paclitaxel

treatment gained higher QALMs than the control group (12.3 vs 6.4 QALM, respectively), but also increased healthcare costs by £18 330 ($US31 894). However, the corresponding ICER was assumed to be cost effective (£37 500 [$US65 250] per QALY) and upon the recommendation of the UK National Institute for Health and Clinical Excellence (NICE) Appraisal Committee, treatment of MBC with trastuzumab + paclitaxel was regarded as justified.

The majority of pharmacoeconomic studies include only one specific indication. Garrison and Veenstra[39] established a dynamic life-cycle model to evaluate the use of trastuzumab in multiple indications (adjuvant and MBC with a HER2-positive expression pattern) to estimate the overall economic value of the agent. Based on publicly available data, QALYs and direct treatment costs were estimated for the product life-cycle of trastuzumab over 18 years. The authors aimed to forecast the volume of use of trastuzumab (given with paclitaxel) over the product life-cycle as well as estimating its cost effectiveness (vs paclitaxel alone) across early-stage and MBC patients from a payer perspective in the US. The model included costs for HER2 testing (immunohistochemistry [IHC] or fluorescence *in situ* hybridization [FISH]), trastuzumab therapy until disease progression, and supervising and treating adverse events. The cost assumptions of trastuzumab treatment in MBC patients were based on current medication costs, survival estimates and utility weights derived from published studies. The authors projected the number of patients treated with trastuzumab as three times lower in MBC than in the adjuvant setting. Accordingly, 161 000 women with MBC would be treated during the entire modelling period. The volume of trastuzumab use and associated costs resulted in an indication-specific ICER of $US85 676 per QALY gained for MBC. The ICER for the overall life-cycle summed to $US35 590 per QALY (ICER for early breast cancer $US26 417 per QALY).

One article examined the health economic outcome of lapatinib in HER2-overexpressing MBC patients.[41] The life-long Markov model comprised information on clinical effectiveness from results of two randomized controlled trials of lapatinib (EGF100151,[56] EGF20002[57]). Published literature was used to gather information on health-state utilities, direct and indirect costs of the therapy, primary adverse events, laboratory tests and costs of disease progression. The model took the US societal perspective. Adding lapatinib to capecitabine therapy yielded additional costs of $US19 630 and 0.12 QALYs. The corresponding ICER resulted in $US166 113 per QALY gained. The sensitivity analyses revealed a lower probability of 2% to reach an ICER below $US150 000 per QALY. Hence, the willingness-to-pay (WTP) threshold is most probably not reachable.

The only cost-effectiveness study on bevacizumab in the first-line treatment of MBC was published by Dedes et al.[40] The study group analysed the economic outcomes of bevacizumab plus paclitaxel versus paclitaxel monotherapy in HER2-negative MBC patients. Study design and data on PFS and OS were based on a randomized clinical trial.[16] With the help of a Markov model, cost effectiveness (expressed as costs per QALY) was assessed. Cost data covered direct costs of chemotherapy treatment, most important adverse events, laboratory tests and disease progression. No indirect costs were taken into account. Utilities were derived from published literature. The combined therapy of paclitaxel + bevacizumab summed to additional per-patient costs of €40 369 in combination with a gain of 0.21 QALYs. Consequentially, the ICER summed to €189 427 ($US278 458) per QALY. The subgroup analysis showed an increasing ICER with age. Due to an improved benefit in efficacy, the ICER of the younger population (aged 27–49 years, ICER €152 823 [$US224 650] per QALY) was considerably lower than that of the older population (aged 65–85 years, ICER €1 226 615 [$US1 803 124] per QALY). The impact of statistical uncertainties around the main input variables were assessed by one-way and probabilistic sensitivity analyses. By varying time to progression (±50%) in the paclitaxel + bevacizumab group, this treatment strategy became dominated. The variation of time (±50%) from progression to death (paclitaxel arm) showed a further considerable influence in sensitivity analysis. In conclusion,

the authors believe that MBC treatment with bevacizumab plus paclitaxel is high and above the generally accepted cost-effectiveness threshold of €60 000 ($US88 200) per QALY gained.

5. Quality Assessment of Key Modelling Issues

Several factors may have an influence on the cost-effectiveness ratio, including funding source, input parameters, under-reporting and the quality of the data integrated in the model.

5.1 Input Parameters

It is of paramount importance to include reliable input parameters in a model. Some articles[25,27,31] mentioned in their study limitations the problem of including data from a small trial sample size. A few articles[21,27] were based on data from abstracts, which is probably not the best source of reliable information. Several trials[21,22,28,58] were powered to show significant results in regard to clinical response or PFS, but not in terms of OS. Hence, those trials may identify significant improvements in primary endpoints, but the gains in survival remain non-significant. Conducting cost-effectiveness analyses based on such results are justified, so long as probabilistic sensitivity analyses are performed to assess the impact of model assumptions not principally related to statistical uncertainties.

5.2 Sensitivity Analyses

Sensitivity analyses are usually carried out in order to estimate the influence of the statistical uncertainties around the model inputs. All analyses included in this review performed sensitivity analyses, but there were major differences in their quality. Most studies conducted deterministic sensitivity analyses to assess the robustness of the base case by varying variables with a direct impact on incremental cost within a certain range (e.g. ±30%). Clearly described probabilistic sensitivity analyses were found in three articles.[21-23] One article[25] used the bootstrapping concept, which differs from probabilistic sensitivity analyses by drawing observations from a data set rather than taking random points in a distribution. However, several studies[26,29,58] did not mention how the sensitivity analyses were performed or what parameters had been used. The robustness of the study results can only be shown if sensitivity analyses have taken all variables into account, especially those with a potential impact on the cost-effectiveness ratio. Critical components in a sensitivity analysis are prices and quantities, functional relationships, the health-related QOL measure and discount rates.

5.3 Perspective of the Analysis

Most studies took the health system perspective (77%). These analyses do not take into account indirect costs, although improved cancer survival enhances the overall social surplus (improved labour force potential). However, a huge percentage of breast cancer patients are of working age. Given this, indirect cost savings and gains in productivity could potentially be considerable and should not be disregarded. Only two articles[22,59] took the societal perspective, in which not only direct and non-direct medical costs but also indirect costs were included.

5.4 Influences on the Cost-Effectiveness Ratio

As shown in this review, the cost effectiveness of trastuzumab was mainly influenced by the drug cost of trastuzumab, outpatient costs and administration costs. The expenditures for administration can be influenced by switching from a weekly administration interval to a 3-weekly schedule. However, the cost-effectiveness ratio identified by Norum et al.[37] did not significantly improve with the 3-weekly interval when compared with the weekly interval. From the patient's point of view, a 3-weekly schedule may yield an enhancement in QOL. However, the weekly administration of trastuzumab has been shown to be superior compared with the 3-weekly course in terms of median PFS (13.4 months vs 8.8 months, respectively).[60] Among conventional chemotherapies, only nab-paclitaxel was studied for different administration schedules. Weekly administration of nab-paclitaxel was associated with more total costs per patient than

3-weekly administration but the improved clinical benefit for the weekly schedule offset these costs.[31]

The acquisition cost was found to be a further influential variable.[37,38] In one analysis, lowering the cost of a trastuzumab flask by about €200 ($US294) meant the mean costs per LYG would equal that achieved with conventional chemotherapy.[38] The standard unit of trastuzumab is a 150 mg vial. It could be argued that providing different sized vials (10 mg, 50 mg) could lower the costs by administering only the exact drug dosage needed.

In addition, the duration of treatment with trastuzumab seems to be a point of discussion. The duration scheme of the targeted therapy in the included studies ranged between 24 weeks (eight cycles)[38] and 1 year[25] or until disease progression.[25,38,39] Prolonging treatment would be associated with increased per-patient costs.[61]

5.5 Comparability of Different Studies

Typically, thresholds for cost-effectiveness ratios for a novel healthcare intervention range from $US50 000 per QALY in the US to £30 000 ($US52 200) per QALY in UK.[62] Although these thresholds are generally regarded as acceptable, the true societal WTP for a new intervention is unknown. It might be reasonable to amend this threshold across higher- and lower-income countries.[63] The included analyses have been conducted in the US/Canada (38%) or Europe (62%). The limitation of comparing studies from various countries lies not only in striking differences in the cost and resources included. There are different approaches and factors that have to be considered when using model-based cost-effectiveness analyses across different geographic regions.[64] For the adjuvant treatment with trastuzumab, Essers et al.[65] presented a possibility of transferring a model-based economic study by assessing criteria and limitations of transferability. However, the main challenge to transferring and comparing results from different studies is mainly the transparency of the methods. Given that several studies[29,32,34,36] did not clearly mention how the economic model was performed (states, cycle length, software used), it is very difficult to compare the model results. Hence, one major problem in evaluating the quality of cost-effectiveness analyses is under-reporting.

5.6 Role of Funding

Several analyses were conducted using funding from pharmaceutical companies that market the analysed drugs.[29,33,35,39,66] Some others did not declare conflicts of interest or funding and had no author affiliated with a pharmaceutical company.[25,32,34,37,38,40,41] Although pharmaceutical company sponsorship has not been found to bias individual health economic studies, it has been reported that it is associated with reduced likelihood of reporting unfavourable results.[67] This suggests that pharmaceutical-sponsored studies are less likely to publish negative results. In fact, among the economic analyses reviewed in this article that reported negative or borderline results regarding cost-effectiveness ratios, all but one[28] were conducted and published by independent research groups.[37,40,41]

6. Discussion

In recent years, many studies addressing the issue of cost and effectiveness of various new regimens for MBC have been published. Developments in the understanding of the molecular pathology of breast cancer have enabled the use of targeted therapies for adjuvant and MBC. At the forefront of development among conventional chemotherapies, potentially more potent drugs (docetaxel, ixabepilone) or established drugs with improved drug delivery formulations (nab-paclitaxel) have entered clinical trials and are successfully used in daily clinical practice. Therapies to target specific cellular pathways expand effective cancer drugs by allowing systematic patient selection. However, the introduction of new drugs for cancer therapy usually increases treatment costs. Pharmacoeconomic analyses are in great demand in order to obtain a better understanding of the cost-benefit ratio of promising cancer drugs.

Among the new conventional chemotherapy regimens, there are some striking differences in trial design and included patient populations that

makes comparisons across the different cost-effectiveness studies difficult. The role of anthracyclines for the adjuvant and metastatic (if not received adjuvantly) treatment of most of the breast cancer types is still not refutable. This is one of the main reasons that most cost-effectiveness analyses focus on second-line therapy after either metastatic or adjuvant anthracycline-containing regimens. At progression or recurrence after anthracyclines, a taxane-containing regimen offers the best response rates and is considered the standard of care.[3] Despite several phase III studies conducted so far, there is still no agreement on the best taxane-containing regimen for second-line chemotherapy. Docetaxel has been shown to be superior to 3-weekly paclitaxel,[44] but a separate trial suggested that weekly paclitaxel is more effective than 3-weekly paclitaxel.[48] On the other hand, docetaxel every week is inferior to 3-weekly docetaxel.[68] Furthermore, nab-paclitaxel has been compared with docetaxel in a phase II trial and showed superiority.[50] While phase II trials are not perfect venues to compare agents, docetaxel was outperformed with regard to overall response rate by nab-paclitaxel in this setting. Similarly, the head-to-head comparison of nab-paclitaxel with standard paclitaxel was a comparison employing 3-weekly paclitaxel and not the more effective weekly regimen.[69] At present, it seems reasonable to consider all three agents useful for MBC, but it is difficult to declare a 'best' agent on objective grounds. Therefore, cost-effectiveness studies should not omit one of the above three regimens. Unfortunately, weekly paclitaxel has been included as a comparator in only two cost-effectiveness studies,[21,58] and results from one study suggested it was not only the most efficient regimen but also the most cost effective.[32]

If economic studies are conducted with poor clinical trial data, poor outcomes will result. There is an ongoing debate over whether cost-effectiveness analyses should only be conducted if the difference in clinical effectiveness between two treatment strategies is statistically significant.[70-72] However, if such data are used in economic studies, adequate sensitivity analyses have to be carried out to evaluate if those input parameters have an influence on the base-case result. Recently, Chan et al.[73] published a review on cost-effectiveness analyses of trastuzumab in the adjuvant setting. The authors concluded that trastuzumab seems to be cost effective in this setting; nevertheless, they suggested further high-quality economic studies with clinical data showing the efficacy of trastuzumab in clinical practice were necessary.

Adjuvant treatment with targeted therapies may reduce the future incidence of MBC. In our review, we did not include any articles that assessed the impact of adjuvant trastuzumab treatment on the reduced drug usage in the future metastatic indication in those patients.[74] From a health economic point of view, the adjuvant and metastatic setting should be evaluated separately, since these are two separate decisions. If lifetime incidence projections make a distinction between newly and previously diagnosed MBC, bias may occur due to epidemiological double counting, which leads to the overestimation of costs and effects of the cancer therapy.[39] On the other hand, most cost-effectiveness studies are based on clinical data of patients naive to the evaluated targeted drug; however, developments in clinical practice are also shifting the usage of targeted therapies to adjuvant therapy. For example, in the case of trastuzumab, the patient population on which Norum et al.[37] based their cost-effectiveness analysis are now virtually non-existent since literally all of them receive trastuzumab in the adjuvant setting. If these patients develop metastases, it is not clear to what extent they will benefit from the same targeted treatment nor which targeted treatment is the most appropriate. Since many new targeted treatments are gaining market approval for various indications in breast cancer and some are also starting to be administered adjuvantly (such as trastuzumab and probably soon lapatinib), cost-effectiveness studies for MBC, according to our review, often do not keep pace with new clinical developments.

Generally, the ICER of targeted non-chemotherapeutics is higher than that of conventional chemotherapeutics. Given different comparators and treatment regimens, the lifetime ICER for trastuzumab varied considerably. The economic

models showed some major differences in their approach to assessing the cost effectiveness of targeted therapies. The economic model used was clearly described in only a few articles.[22,23] The two publications[22,23] focusing on bevacizumab and lapatinib, respectively, showed no favourable ICER. Those two studies were based on clinical trial results and clearly described the model methodology, the parameters included and the analyses performed. Furthermore, the authors did not receive any funding from the pharmaceutical industry.

Cost-effectiveness thresholds vary between countries. Usually, threshold values of $US20 000, $US50 000 or $US100 000 per QALY or LYG are applied.[75] In the metastatic setting, several studies on antibody-based targeted therapies indicated an unfavourable ICER.[37,40,41] In spite of this, trastuzumab has been established in clinical practice in both the adjuvant and metastatic setting.

There are some limitations to this systematic review. The review excluded articles written in languages other than English. Furthermore, results presented at meetings (abstracts) were not included. In addition, the search was limited to the database and the keywords described, which may have omitted some cost-effectiveness analyses.

Cost-effectiveness analyses on new therapies for MBC are rarely found in the published literature and high-quality economic models are needed. For agents such as bevacizumab or nab-paclitaxel, the clinical benefit in terms of OS is still under investigation and it remains to be seen if these new therapies will be established in clinical practice as routine therapies.

7. Conclusions

We conducted a systematic review of cost-effectiveness studies of chemotherapy and targeted regimens for MBC. In this setting, only a few studies were found with varying conclusions. Studies on cytotoxic agents showed mostly favourable cost-effectiveness ratios, while those on targeted therapies showed both favourable and non-favourable ratios. The cost-effectiveness ratio seems to be dependent on the drug price, the extent of improvement in survival rates, and the administration schedule. However, the interpretation of cost-effectiveness studies should not only be limited to the value of the ICER achieved. The quality of the data and the key modelling parameters included in the analysis should be considered. However, in the case of trastuzumab, the patient population included in the cost-effectiveness analyses no longer reflects HER2-positive MBC patients, as almost all current patients will have already received trastuzumab adjuvantly. Many healthcare systems will have problems with accepting the high cost-effectiveness ratios of some expensive cancer treatments. Trastuzumab, for example, is widely justified due to its clinical benefit. Pharmacoeconomic decisions about the management of new agents such as bevacizumab or nab-paclitaxel will appear as soon as enough clinical evidence is available.

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3. *Predictive testing for KRAS and BRAF mutations in the treatment of metastatic colorectal cancer – A cost-effectiveness analysis from the Swiss perspective*

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This study represents the second part of my PhD study programme. This project was developed during the last year of my PhD based on the background and experience of the first breast cancer model. All ideas, the Markov model, the manuscript content and structure were developed and defined by me and my direct and indirect supervisors Prof. med. Thomas D. Szucs, Prof. Dr. med. Holger Moch and PD Dr. Matthias Schwenkglenks.

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KRAS and BRAF mutation analysis in metastatic colorectal cancer: a cost-effectiveness analysis from a Swiss perspective

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ABSTRACT

Purpose – monoclonal antibodies against the epidermal growth factor receptor (EGFR), such as cetuximab, have led to significant clinical benefits for metastatic colorectal cancer (mCRC) patients but have also increased treatment costs considerably. Recent evidence associates KRAS and BRAF mutations with resistance to EGFR antibodies. We assessed the cost-effectiveness of predictive testing for KRAS and BRAF mutations, prior to cetuximab treatment of chemorefractory mCRC patients.

Experimental Design – a life-long Markov simulation model was used to estimate direct medical costs (€) and clinical effectiveness (quality adjusted life years, QALYs) of the following strategies: KRAS testing, KRAS testing with subsequent BRAF testing of KRAS-wildtypes (KRAS/BRAF), cetuximab treatment without testing. Comparison was against no cetuximab treatment (reference strategy). In the testing strategies, cetuximab treatment was initiated if no mutations were detected. Best supportive care was given to all patients. Survival times/utilities were derived from published randomised clinical trials. Costs were assessed from the perspective of the Swiss health system.

Results – Average remaining life-time costs ranged from €3'983 (no cetuximab) to €24'771 (no testing). Cetuximab treatment guided by KRAS/BRAF achieved gains of 0.252 QALYs compared to the reference strategy. The KRAS testing strategy achieved an additional gain of 0.001 QALYs compared to KRAS/BRAF. KRAS/BRAF testing was the most cost-effective approach when compared to the reference strategy (incremental cost-effectiveness ratio: €67'779/QALY).

Conclusion – new predictive tests for KRAS and BRAF-status are currently being introduced in pathology. Despite substantial costs of predictive testing, it is economically favourable to identify patients with KRAS and BRAF wildtype status.

INTRODUCTION

Despite substantial progress in surgery and chemotherapy treatments, patients with metastatic colorectal cancer (mCRC) generally have a poor prognosis. Monoclonal antibody therapy targeted against the epidermal growth factor receptor (EGFR), e.g. cetuximab (Erbitux®, Merck KGaA, Germany) has led to significant clinical benefits in mCRC patients[1]. Overexpression and activation of EGFR and transduction of activation signal play an important role in tumor progression[2, 3]. Recent evidence suggests that genetic alteration of downstream regulator proteins like KRAS and BRAF are associated with lack of response to antibody therapy[4-10]. Prevalence of the KRAS proto-oncogen in mCRC is 30-45%[6, 11-14], whereas about 10% of wild-type KRAS tumours show BRAF-V600E (BRAF) mutation[13, 15]. Mutations in KRAS and BRAF occur in a mutual exclusive manner in CRC cells[16].

KRAS and BRAF gene status can be assessed by formalin-fixed, paraffin-embedded tissue. Several methods are available to detect oncogenetic mutations of KRAS and BRAF like, e.g., direct dideoxy-sequence analysis (sequencing method), pyrosequencing or allele-specific real-time PCR or others[17-21]. However, the cycle sequence method is the "gold standard" for KRAS analysis[22]. In Swiss laboratories, DNA sequencing after Sanger (dye terminator cycle sequencing) is generally used[23]. Given high sensitivity and perfect specificity of these assays, false negative or false positive results are scarce, but cannot be ruled out entirely.

Recently, the American Society of Clinical Oncology issued a provisional clinical opinion on testing for KRAS mutation in mCRC patients, stating that KRAS mutation should be assessed in patients with mCRC who are candidates for EGFR antibody therapy[24]. In case of a KRAS mutation, antibody treatment should not be administered[24]. However, international guidelines for performing and assessing KRAS mutations are still being developed[25]. Testing for BRAF mutation has just started in some laboratories. Recent clinical evidence supports BRAF mutation analysis, although the available testing procedures are fairly expensive.

Predictive testing helps selecting the treatments patients will most benefit from. Additional costs of novel predictive tests like KRAS and BRAF have to be balanced against cost savings associated with avoiding treatment of patients who will predictably not respond to antibody treatment. Markov models have already been used in the metastatic breast cancer setting to measure the cost-effectiveness of different testing strategies[26, 27]. However, the economic consequences of testing for KRAS and/or BRAF mutations in mCRC patients have not yet been studied. The objective of this analysis is to assess the cost-effectiveness of testing for KRAS/BRAF mutations, prior to cetuximab treatment of chemorefractory mCRC patients, from a Swiss health care system perspective.

METHODS

Overview of mCRC disease model

Based on a previously used modelling framework[28], we constructed a Markov state-transition model with an one-months cycle length to assess the economic consequences associated with each testing strategy. Effectiveness was assessed in terms of quality-adjusted life-years (QALYs). On this basis, incremental cost-effectiveness ratios (ICERs) were calculated. The time horizon of the analysis was life-long.

Costs were assessed from the perspective of the Swiss health care system. Accordingly, non-medical direct costs and indirect costs were not taken into account. Direct medical costs included drug costs, costs for predictive testing (where applicable), diagnostic procedures and hospitalization. Costs and effects were discounted at an annual rate of 3%[29]. Costs are expressed in Euros (€). An exchange rate of €1.00 = CHF1.50 was used (February 2010).

The Markov model was implemented in TreeAge Pro® 2009 (TreeAge Software Inc, Williamstown, MA, USA).

Patient population studied

The model followed a hypothetical cohort of chemorefractory, mCRC patients aged 50 years (45% female, 55% male)[30]. It was assumed that 70% of patients were wild-type KRAS and that 8% of this group (6% of the total) had a BRAF mutation status[8, 16, 31, 32]. The eligibility criteria of our patient population were defined by the phase III National Cancer Institute of Canada Trial Group CO.17 (CO.17) study[33]. In brief, patients had advanced colorectal cancer (Eastern Cooperative Oncology Group performance status 0-2) with immunohistochemically detectable EGFR expression. They were chemorefractory and no other anticancer therapy was available[33].

The influence of all-cause mortality on the survival experience of the cohort was modeled using Swiss life tables[34].

Strategies compared

Following testing strategies were assessed: KRAS alone and a sequential approach with BRAF testing of all KRAS wild-type patients. Patients with KRAS wild-type (in the KRAS alone strategy), or with KRAS wild-type/BRAF wild-type status, received cetuximab. Best supportive care (BSC) was administered to patients with KRAS mutation or BRAF mutation. Costs and effects of the no cetuximab treatment strategy served as reference values. Administering cetuximab to the entire patient population without prior predictive testing (no testing strategy) was added to estimate the overall benefit of predictive testing.

The occurrence of false positive and false negative test results may have severe consequences for the affected patients. Information on sensitivity and specificity of mutation analyses (sequencing method) were derived from published literature[22]. The probabilities of false positive false negative test results were assumed to be the same for KRAS and BRAF, each taken by itself. Sensitivity and specificity of the KRAS and BRAF testing strategy were evaluated according to the "believe-the-positive" approach, i.e. the combined result was positive if one test indicated a positive result (mutation). Both tests were regarded as conditionally independent (Table 1)[35].

Disease stages and clinical data sources

The Markov model was build up with three commonly exhaustive and mutually exclusive health states: stable/responsive disease, disease progression and death. All patients entered the model in the stable state and they could remain stable or progress. Patients with progressive disease could remain in this state or die (Figure 1).

Transition probabilities were assessed from median time to progression and median time to death, as observed in the phase III randomized CO.17 trial[32, 33]. The treatment effect, namely transition probabilities for patients with KRAS wild-

type and KRAS mutation, was modeled dependent on mutation status and treatment given[4-6, 9, 32]. Monthly survival rates and median time to disease progression were taken from the CO.17 trial, which compared BSC plus cetuximab with BSC[33]. Data for transition probabilities of patients with a BRAF mutation status under cetuximab treatment were extracted from retrospective analyses of mCRC patients treated with cetuximab in different centres[8, 9]. We assumed that patients with BRAF mutation receiving BSC would have the same transition probabilities as patients with a KRAS mutation in the CO.17 BSC arm (Table 2).

Utilities

Preference-based measures of health-related quality of life were available from the CO.17 study. They were prospectively collected using the self-reported Health Utility Index Mark 3 (HUI3) questionnaire[36, 37]. Mean utility in the wild-type cetuximab group (stable disease state, responding to treatment) was 0.72 (CI 0.49-0.95) at baseline and increased over time (0.77; CI 0.55-0.99 at week 24). Mean utility in the BSC group was 0.71 (CI 0.47-0.95) at baseline and decreased over time (0.70 at week 24; CI 0.56-0.94)[37]. In our model, the latter values were applied to both wild-type and mutant patients in the stable disease state without cetuximab treatment and to mutant patients with cetuximab. For patients in a progressed state, a value of 0.5 (0.45-0.72) was assumed[38-40].

Medical resource use

Best supportive care

BSC was given to all patients. Given that patients were assumed to be chemorefractory, BSC therapy consisted mainly of palliation of symptoms and improvement of quality of life[33, 41]. Concomitant therapy (antibiotics, opiates, steroids, antithrombotics, antidiarrheals, antiemetics, blood formation products) and episodes of hospitalization were assumed to be the same for all patients, during a given period of time (e.g. month of follow-up)[37]. Quantities of medical interventions such as diagnostic and therapeutic interventions were assessed on the basis of published literature[37]. Length of average hospital stay for colorectal patients was based on data provided by the Swiss Federal Statistical Office (Appendix.1).

The model considered differences in medical resource use between the treatment groups (reference and cetuximab group) which arose from different survival times.

Reference group

All patients in the reference strategy (no cetuximab) received BSC only (as described above). Concomitant therapy, diagnostic ultrasound and palliative surgery including hospitalization were used in these patients. For the evaluation of disease status, all patients had a monthly medical consultation, chest radiologic imaging and cross-sectional imaging every eight weeks, and a magnetic resonance imaging (MRI) at baseline (Appendix.1)[33].

Cetuximab group

Patients with wild-type KRAS/BRAF status received BSC (as described above) plus cetuximab; in the no testing strategy all patients received BSC plus cetuximab. Cetuximab was given until disease progression or intolerable toxicity. For tumor evaluation, diagnostic tests were used as described above (Appendix.1)[33]. The cetuximab treatment group was assumed to have physician outpatient assessments every week due to the infusion schedule of the drug. The dosing regimen of cetuximab matched the treatment schedule described elsewhere[32, 33]. An intravenous loading dose of 400mg/m^2 body surface area was followed by a weekly maintenance dose of 250mg/m^2. Adjusting for the gender distribution in Swiss incident cases[30], the model assumed a loading dose and a maintenance dose of 706mg and 441mg, respectively. Administration costs for drug infusion were taken into account.

Unit costs

Costs for laboratory tests, diagnostic interventions and drug administration time were estimated based on resource utilization, and were multiplied by unit costs drawn from the official Swiss tariff list (Tarmed)[42]. Drug costs were based on official Swiss pharmacy prices (Appendix.1)[43]. Average hospital length of stay was obtained from Swiss hospital statistics[44, 45]. According to the Swiss Federal Office for Statistics, 50% of hospital per diem costs were paid by Statutory Health Insurance, the rest is covered by cantonal authorities[45, 46]. Hence, the hospitalization costs were computed on this basis (case-based lump sum €1'127 plus daily rate of €152)[44]. Concomitant therapy was assumed to be the same for all patients, hence those costs were not included[37].

Sensitivity analysis

Deterministic sensitivity analysis

One-way sensitivity analyses assessed the robustness of the base-case results. Parameters subject to statistical uncertainty (utility values, sensitivity and specificity of mutation analyses) were varied within their 95% confidence intervals (CIs)[47]. The prevalence of KRAS and BRAF mutations was varied between 0.25-0.40[17, 48] and 0.05-0.22[15, 49], respectively.

Variables not subject to statistical uncertainty were considered in scenario-analyses. Variables with direct impact on the ICER were varied by ±30%: costs of cetuximab, of mutation analyses, and of palliative care of metastatic disease. Medical resource use (diagnostic interventions) was varied in the BSC group only. Discount rates of 0% and 6% were additionally assessed

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA; second order Monte Carlo simulation) estimated overall parameter uncertainty around the base-case by using 10,000 sets of parameter values, which were randomly sampled from statistical distributions reflecting the ranges of variation used in deterministic sensitivity analysis[44]. Beta-distributions were used for KRAS mutation/BRAF mutation prevalence, and test sensitivity and specificity. Triangular distributions were used for utility during stable disease and after progression. Gamma-distributions were used for median survival times and median time to progression. Unit costs were not subject to uncertainty and not included in the PSA[42].

RESULTS

Base-case analysis

Cost

In the base-case analysis, the addition of cetuximab to BSC increased costs considerably. As cetuximab use was restricted to patients who benefited most from therapy, the increase in costs in the testing strategies was distinctly lower than in the no-testing strategy. The costs of mutation

analysis (€394 per analysis) were overcompensated by savings associated with the restriction of cetuximab administration to expected responders. Average lifetime per-patient costs were €21'092, €21'641 and €24'771 in the KRAS/BRAF, KRAS and no testing strategies, respectively. If KRAS/ BRAF testing was used, per-patient savings would be €549 and €3'679 compared to KRAS testing and the no-testing strategy (Table 3).

Effect

Given imperfect sensitivity and specificity of the mutation analyses, different testing strategies led to different clinical outcomes (Table 1). Some patients had false negative or false positive results and hence, received cetuximab or BSC treatment inappropriately, translating into QALY loss. Accordingly, the no testing strategy led to the highest QALY result (0.700 QALYs/patient). The KRAS/BRAF and KRAS testing strategies accrued 0.696 and 0.697 QALYs, respectively. The lowest result was observed in the reference strategy with no cetuximab use (0.443 QALYs) (Table 3).

Incremental cost-effectiveness

The least costly and least effective approach was the reference strategy (no cetuximab) (Table 3). Testing for KRAS and BRAF mutations led to average per-patient costs of €17'109 and a quality-adjusted survival time of 0.252 QALYs, translating into an ICER of €67'779/QALY gained, compared to no cetuximab. Testing for KRAS only led to an ICER of €466'725/QALY versus KRAS and BRAF testing. The regimen with no predictive testing showed an even less favourable ICER (€1'076'591/QALY versus KRAS) (Figure 2).

In Switzerland, about 4011 new colorectal cancer patients are registered annually (average 2003-2006)[30]. If 25% (1'003) of these patients developed metastatic disease[50, 51], KRAS and BRAF testing would lead to annual direct cost savings of €550'666 and a loss of 1.18 QALYs compared to KRAS. In comparison with no testing, KRAS and BRAF testing would save €3'690'042 and imply a loss of 4.10 QALYs, per year. Compared to the no cetuximab strategy, the usage of KRAS and BRAF mutation analysis, with subsequent cetuximab administration where indicated, would require an annual net investment of about €17.2 million to acquire a gain of 253 QALYs.

Sensitivity analysis

The results of the deterministic sensitivity analyses indicated that varying the utility value for progressive disease had the strongest impact on the ICER (Appendix 2). The rank order of strategies was sustained in all situations assessed. The impact of the scenario analyses on ICER results was minor (Appendix.3).

In PSA, KRAS and BRAF testing was the dominant strategy over a willingness to pay range of €10'000-€80'000 per QALY gained. Beyond €80'000/QALY, KRAS became the preferred strategy (Figure 3). Further PSA results are presented in Appendix.4.

DISCUSSION AND CONCLUSION

This present work is the first study addressing the cost-effectiveness of predictive KRAS and BRAF testing, prior to cetuximab administration to mCRC patients. Testing for KRAS and BRAF status with subsequent cetuximab treatment of patients with confirmed wild-type showed the most favourable ICER, of €67'779/QALY gained compared to no cetuximab use. Robustness of results was ascertained in a wide range of sensitivity analyses.

According to the revised prescribing information, mCRC patients with KRAS mutations are not recommended to receive cetuximab, as they are unlikely to benefit from anti-EGFR drugs[52]. Given this, KRAS assessment is routine practice in Swiss pathology laboratories. Recently, testing for BRAF mutations has been introduced as a result of growing evidence of predictive and prognostic value in mCRC patients considered for antibody treatment[8, 16, 53, 54]. Our results add to the rationale for these approaches.

Predictive tests need to have appropriate sensitivity and specificity. For KRAS and BRAF, sequencing analysis is frequently used, as was assumed in our model[55]. Direct sequencing analysis is characterised by its potential to detect all mutations, leading to very high specificity[23]. On the other hand, this method may feature a lack in sensitivity compared to other techniques[55]. In consequence, some patients with KRAS or BRAS mutations may still receive anti-EGFR treatment.

Further EGFR downstream regulators have been associated with lack of response to monoclonal antibodies in mCRC, e.g. loss in PTEN expression[3] or PIK3CA mutation[11]. However, the evaluation of PTEN requires more standardization and is not yet ready for the clinical setting[11, 56]. Furthermore, the real predictive value of PIK3CA mutations is not firmly established[57].

Cost-effectiveness thresholds for clinical interventions vary between countries. Threshold values of $50'000-$100'000 (€38'500-€77'000) per QALY gained (USA) or £20'000-£30'000 (€23'000-€35'000) per QALY gained (UK) are regarded as realistic[58]. Mittmann et al. conducted an economic evaluation of cetuximab therapy for mCRC patients[37]. In a sub-analysis, they assessed cetuximab versus BSC in KRAS wild-type patients. The resulting ICER of €144'360 (CI: €100'737-€258'896) per QALY gained is unfavorable compared with our result. The authors found a QALY difference of 0.18, which is about half of our estimated QALY gain. A likely reason for this apparent discrepancy is that Mittmann et al. restricted the time horizon of their analysis to the observation period of the CO.17 trial (18-19 months, during which 77% and 82% patients in the cetuximab and BSC arms died, respectively)[33, 37]. In contrast, our model used a life-long time horizon, in line with good health economic practice for the assessment of interventions with life-long consequences or an impact on survival[59]. Taking into account the full survival experience of all patients inclusive of longer-term survivors, using appropriate modeling techniques, lead to a higher accumulation of QALYs gained and is likely to explain our more favorable ICER results.

A further health economic analysis found an ICER of about €70'000/QALY for cetuximab in combination with chemotherapy[41]. This analysis did not differentiate between KRAS mutant and wild-type patients, although it was mentioned by the authors that factors specific to the patient population should be considered.

Some limitations of our study are related to data availability. Starting with a clearly defined patient population, we tried to identify the most appropriate model inputs currently available from the literature. However, clinical evidence from biomarker-based randomized trials is scarce in the colorectal cancer setting. Hence, clinical and utility data originated from few studies conducted outside Switzerland[8, 32, 33, 37]. As one consequence, available quality of life and utility data allowed to

differentiate on the basis of cetuximab treatment versus BSC, but not on the basis of mutation status. Given that both BRAF and KRAS mutation is associated with a similar lack of response to cetuximab, similar quality of life was assumed in non-responders as in BCS-treated patients. Furthermore, differences in QALY results originated mainly from differences in survival time due to mutation status and treatment given. This instance has been fully incorporated into our analysis. Information on clinical resource use was primarily clinical trial-based and deviations from routine practice patterns may occur. However, varying the use of diagnostic procedures in the BSC group did not impact the main result.

Of note, this economic analysis is focusing on patients with late stage, chemo-refractory cancer. Latest evidence implies that cetuximab first-line treatment of mCRC leads to significant response in KRAS/BRAF wild-type patients[60]. However, BRAF mutation seemed to have no impact on response to the antibody, suggesting that BRAF mutation may not have the same predictive value in first-line and chemo-refractory tumors.

In conclusion, testing for KRAS and BRAF mutations prior to cetuximab treatment of chemorefractory mCRC patients is clinically appropriate and economically favorable, despite high costs for predictive testing.

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Table 1.Strategies and characteristics of predictive tests

Test strategy	Test result	Treatment	Sensitivity (95%CI)	Specificity (95%CI)	Ref.
KRAS	KRAS wt	CET	0.955 (0.917-0.979)	0.997 (0.982-1.0)	[22]
	KRAS mt	BSC			
KRAS and BRAF**	KRAS wt/ BRAF wt	CET	0.998 (0.993-0.9996)	0.994 (0.964-1.0)	[22, 35]
	KRAS wt/ BRAF mt	BSC	0.998 (0.993-0.9996)	0.994 (0.964-1.0)	
	KRAS mt	BSC	0.955 (0.917-0.979)	0.997 (0.982-1.0)	
No test	-	All CET	-	-	-
No CET (no test)*	-	All BSC	-	-	-

*Reference strategy, **BTP: Belief the positive. One positive test result is sufficient for an overall positive result. The overall result is negative if both tests are negative.

BSC, best supportive care; CET, cetuximab; Mt, mutant; wt, wild-type.

Table 2. Clinical input parameters: survival according to mutation status and treatment strategy

Mutation status				Ref.			Ref.
	KRAS	wt			wt	mt	
	BRAF	wt	mt		-	-	
Median OS (months)	CET	14.8	6.5	[8]	9.5	4.5	[32]
	BSC	4.8	4.6	[32]	4.8	4.6	[32]
Median PFS (months)	CET	7.85	2	[8]	3.7	1.8	[32]
	BSC	1.9	1.8	[32]	1.9	1.8	[32]

BSC, best supportive care; CET, cetuximab; Mt, mutation; wt, wild-type; PFS, progression free survival; OS, overall survival.

Table 3. Base-case cost-effectiveness analysis of different testing strategies

Test strategy	Lifetime cost per person	Lifetime efficacy	Incremental costs*	Incremental efficacy*	ICER
Unit	€	QALY	€	QALY	€/QALY
Reference (No CET, no test)	3'983	0.4430	-	-	-
KRAS and BRAF	21'092	0.6954	17'109[a]	0.2524[a]	67'779[a]
KRAS	21'641	0.6966	549[b]	0.0012[b]	466'725[b]
No test	24'771	0.6995	3'130[c]	0.0029[c]	1'076'591[c]

*Relative to the strategy with the next lower cost

[a]Compared to the reference strategy (no CET), [b]Compared to KRAS/BRAF, [c]Compared to KRAS

CET, cetuximab; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

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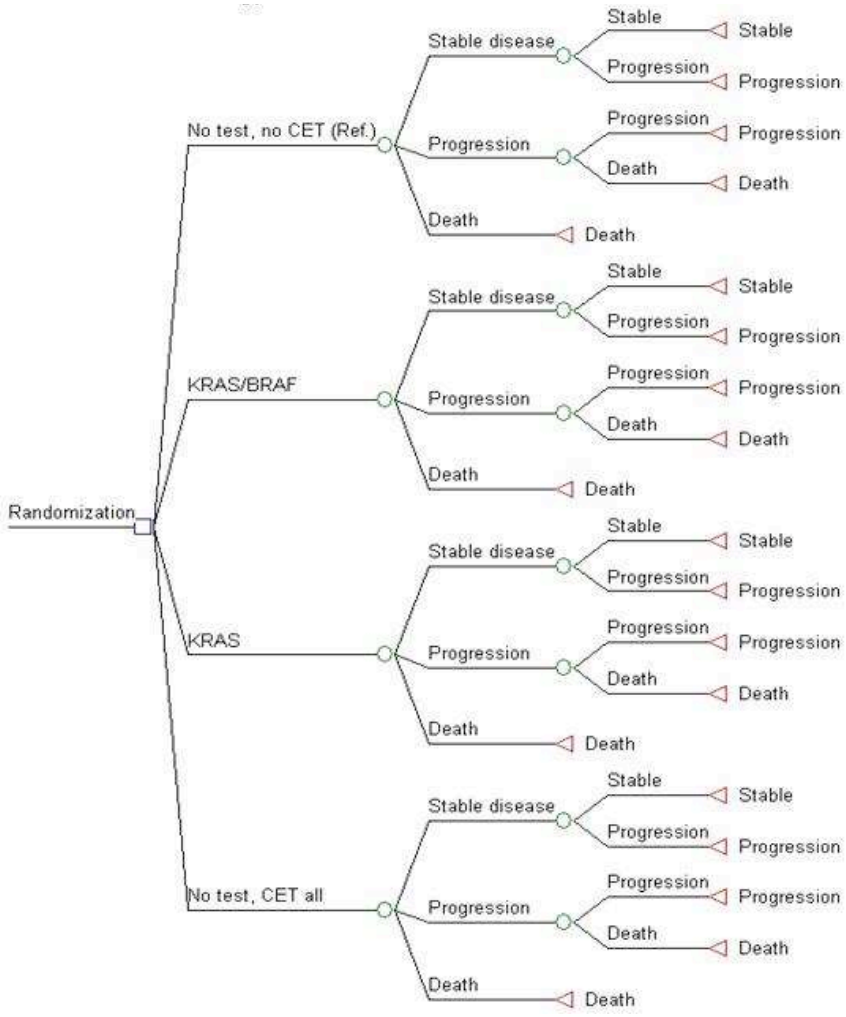
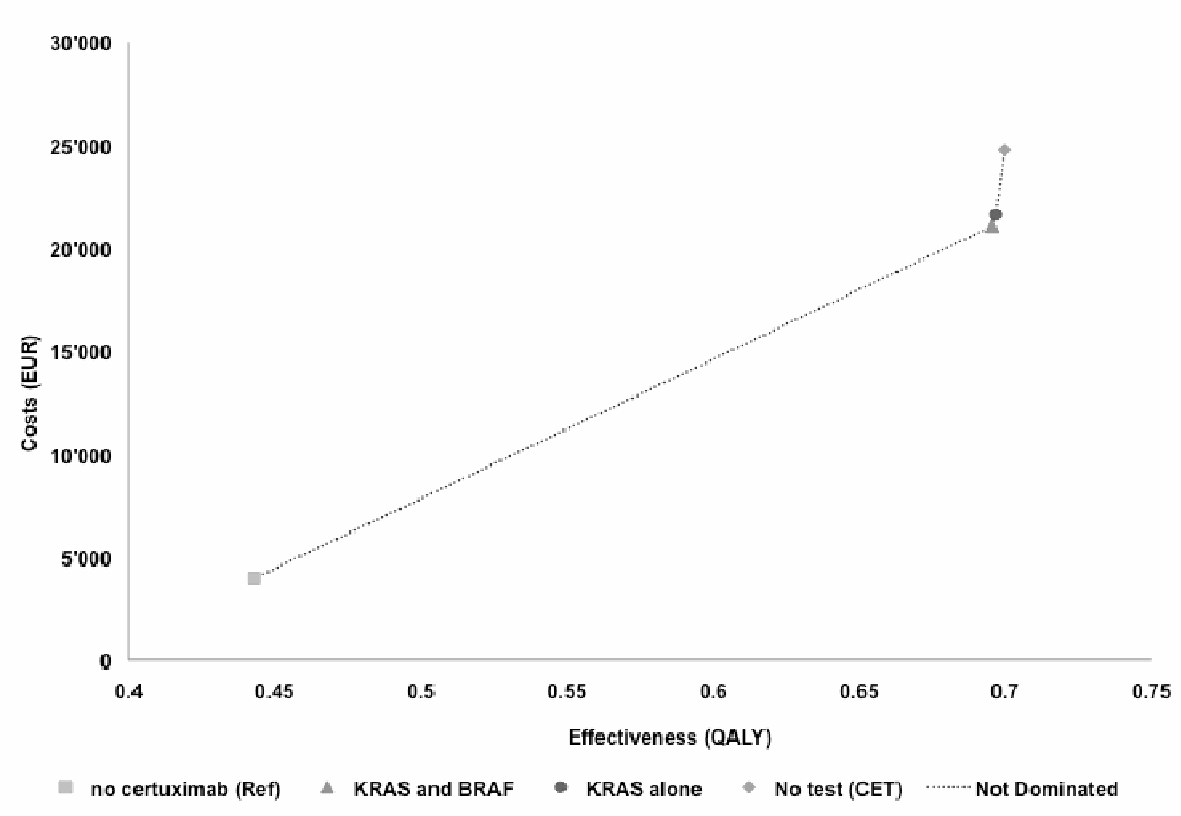
Figure 1. Overview of Markov Model



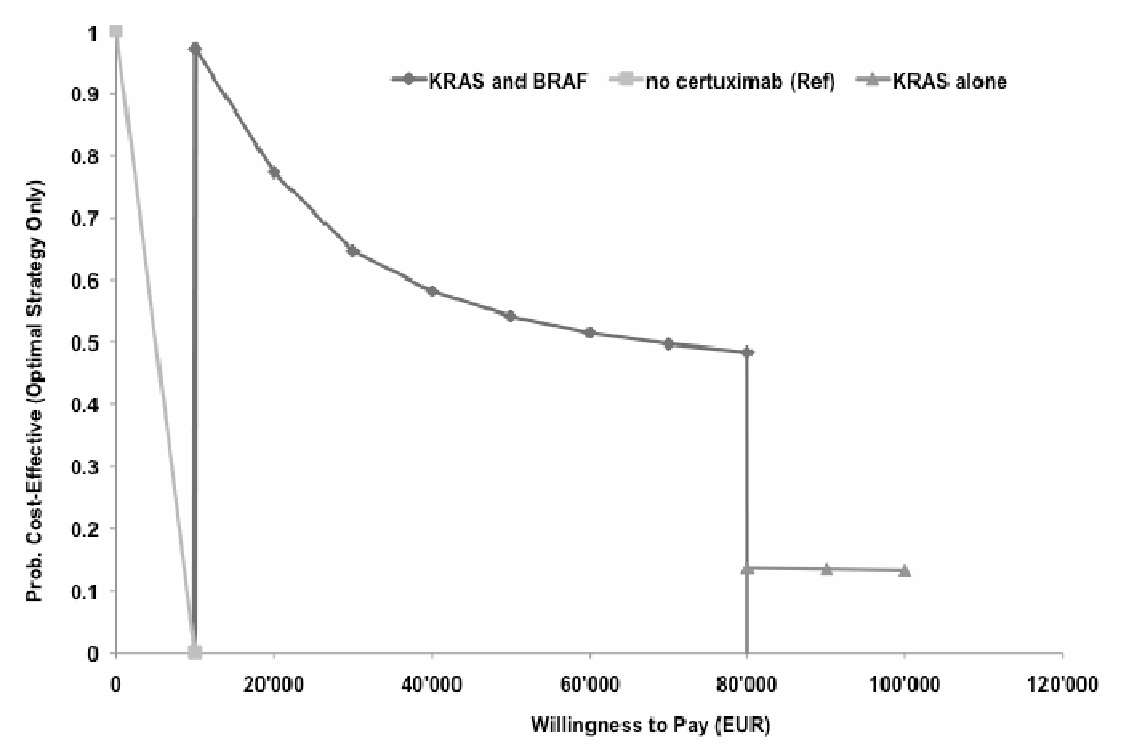
CET, cetuximab; Ref, reference strategy

Figure 2. Base case cost-effectiveness analysis



CET, cetuximab; Ref, reference strategy; QALY, quality adjusted life year

Figure 3. Probabilistic sensitivity analysis (Acceptability frontier*)



*The cost-effectiveness acceptability frontier shows the PSA-based probability of strategies being cost-effective. For different willingness to pay thresholds, different strategies are optimal. For each threshold, only the probability for the optimal strategy is shown. The no-testing strategy (not displayed in the figure) becomes at no threshold value the preferred strategy. Ref, reference strategy; prob, probability

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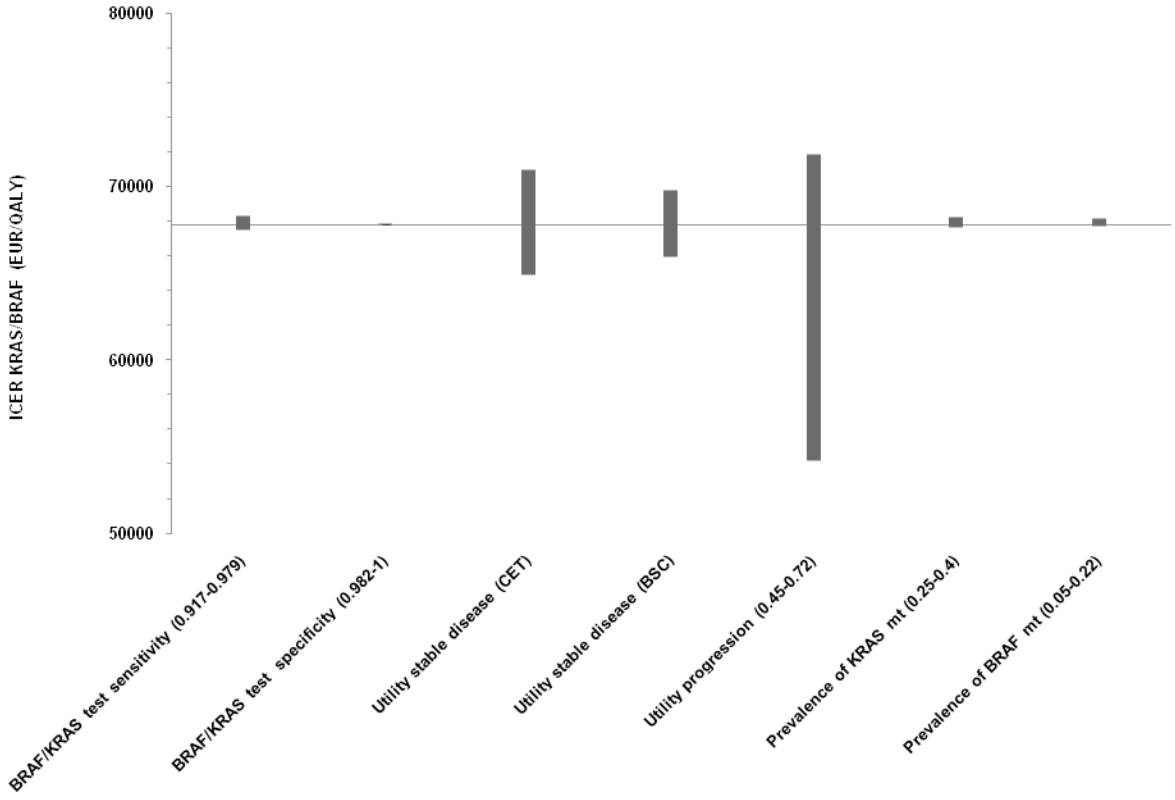
Appendix 1. Medical resource use and cost data

Type of resource	Dose / units used	Unit cost (€)	Ref.
Cetuximab	706mg per week[1)]	4'840 first month	[43]
	441mg per week[2)]	4'208 subsequent months	
KRAS / BRAF mutation analysis	1 (once per patient)	394	[42]
Medical consultation (15')	1-4 per month[3)]	13	[42]
Administration of Cetuximab	1 (90 min) per week	50	
Average stay in hospital	16.3 days per year[4)]	3'598	[44, 45]
Magnetic resonance imaging	1 (once per patient)	146	[42]
Radiologic imaging (chest)	0.5 per month	74	[42]
Cross-sectional imaging	0.5 per month	108	[42]

[1)] starting dose
[2)] maintenance dose
[3)] cetuximab and BSC patients were assumed to require weekly and monthly outpatient visits, respectively.
[4)] average length of stay of patients admitted to a Swiss hospital with a diagnosis of ICD-10 C180-200 , during 2005.

Appendix 2. Results of the deterministic sensitivity analysis in regard to parameter uncertainties

BSC, best supportive care; CET, cetuximab; Mt, mutation



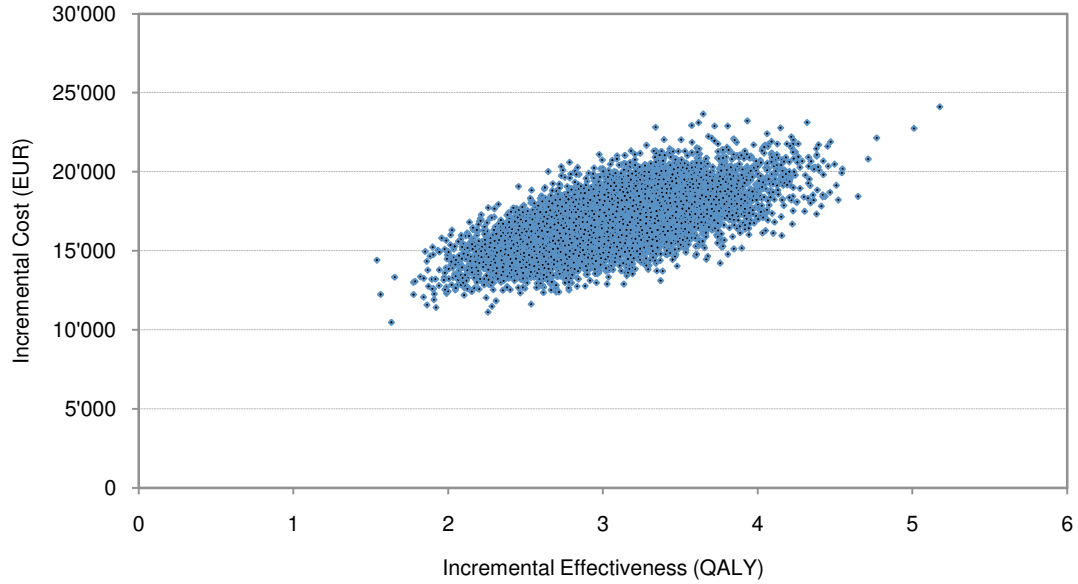
Appendix 3. Deterministic sensitivity analysis of incremental costs (EUR) per QALY gained (ICER) (Scenario analysis)

Test strategy	KRAS and BRAF vs. reference*	KRAS vs. KRAS and BRAF	No testing vs. KRAS
Base-case	67'779	466'725	1'076'591
Price cetuximab +30%	84'942	637'545	1'413'807
Price cetuximab -30%	50'615	295'906	739'375
Price predictive test +30%	68'177	431'559	1'056'265
Price predictive test -30%	67'381	501'892	1'096'918
Palliative care (Basic cost metastatic disease) +30%	70'197	467'609	1'075'814
Palliative care (Basic cost metastatic disease) -30%	65'360	465'841	1'077'368
Reducing diagnostic interventions in reference group (BSC)**	66'955	474'004	1'092'644
Discount rate +3%	69'676	474'153	1'072'802
Discount rate -3%	65'902	459'064	1'080'570

* No Cetuximab, no test

**Assuming that patients had magnetic resonance imaging, radiologic imaging and cross-sectional imaging at the time of treatment decision (model entry), but no subsequent diagnostic tests.

Appendix 4. Incremental cost-effectiveness scatterplot of KRAS and BRAF versus no certuximab (QALY, quality adjusted life year)



Part V – General discussion

In Switzerland, cancer is the second most common cause of death, with about 31'000 new cases and 15'000 cancer related deaths every year. Men are mainly affected by prostate, lung and colon cancer, whereas in women breast, colon and lung cancer are the most common types[161].

In recent years, health-care payers have been faced with increasing cost pressure[162]. According to the Federal Office of Public Health (FOPH), the Swiss health system accounted for about CHF 55.3 billion (€ 42.1 billion) in 2007. Correspondingly, 10.8% of the gross domestic product (GDP) was spent on the health care sector. This proportion has increased by about 5.4 percentage points since 1970[163]. The financial burden of cancer is considerable. Cancer drugs account for about 10% of the total costs of prescription only medicaments in Switzerland[164]. One attempt to respond to this problem in the field of oncology is the development of biomarker-based and pharmacogenetic approaches, including new diagnostic innovations. These approaches strive for selecting patient sub-groups who will most probably obtain a maximal clinical benefit, while reducing possible adverse events among those who are less prone to benefit from a given treatment. Withholding potential cancer therapies from patients may result in excess recurrence rates and deaths. However, overuse of the drug by administering it to non-responding patients yields in avoidable risk of side effects and incurs unnecessary health care costs[165] [102].

The primary criteria for applying diagnostic assays are test performance and predictive and/or prognostic values. This means that the choice of the test strategy or an assay depends upon the level of information on the relative response rate of selected patients. Costs, availability and ease of utilisation are of secondary consideration[79]. The use of predictive tests has emerged and implicates the potential of improving the quality and efficiency of targeted health care[166]. Clinically useful predictive tests with reasonable sensitivity and specificity to predict drug-response are one cornerstone in achieving a cost–effective implementation of new treatment strategies in oncology.

Markov models can assess clinical benefits and adverse effects of therapies measured in quality-adjusted life-years; the observed response to the therapy with various testing methods; and the cost of testing, monitoring, and treatment. This is particularly important for decision making in selecting test strategies with different sensitivities or specificities.

1. Cost-effectiveness of HER-2 test assays

There is a long debate in the literature, which HER-2 test should be performed. Arguments pro and contra specific tests or their combinations include sensitivity of the tests, reliability in FFPE tissue samples, treatment response, reproducibility between laboratories, and health cost considerations[79]. Both, erroneously treating women whose breast cancers lack HER-2 or failing to treat HER-2 positive women, should be prevented.

There is only little evidence about the usage of HER-2 tests and their health economic implications. This is not only true for Switzerland, but also for other European countries or the USA. A recent review

identified cost-effectiveness studies of HER-2 test strategies in the clinical practice of the USA[166]. By screening 621 studies, only four publications matched the search criteria. Studies examining the health economics of HER-2 tests in the adjuvant setting were not identified. Only one study assessed several potential testing strategies in the metastatic breast cancer setting[167]. In our publication[168], we have addressed the existing cost-effectiveness studies in more detail.

In the first part of my study programme, the costs and clinical implications of various HER-2 testing regimens were modelled, prior to antibody-based cancer treatment (i.e. trastuzumab) of adjuvant breast cancer patients. The study evaluated the costs and effects of assessing the HER-2 status by IHC and/or FISH to identify patients who are unlikely to respond to therapy from a Swiss healthcare perspective. The study clearly favours the FISH assay as the main strategy (ICER: € 12'245/QALY when compared with no trastuzumab use)[168]. The present analysis was the first to address the health economic impact of HER-2 testing in Switzerland.

1.1. Limitations of the study

There are some limitations of the study which should be mentioned. One limiting factor is the available data sources. Starting with a clearly defined patient population, I tried to identify the most suitable model inputs available from the existing literature. Data from different sources were selected for the modelling. For some of the parameters existing data vary to some extent (e.g. test characteristics of HER-2 by FISH or IHC). The crucial key element of an economic study is the selection of a reliable data basis which is incorporated in the final model. Sensitivity and specificity of the HER-2 testing, but also the utilities of each health state were critical key elements in the outcome of the analysis. Various sensitivity analyses have been performed to assess the robustness of the study result. Key limitations were addressed in the publication[168] but the level of detail was restricted due to word limitations. For giving the full picture of all critical points, I am going into more detail in the following section.

I performed a thorough literature review and was in close collaboration with clinicians and experts in the field of oncology. HER-2 positive patients are well known to have a worse prognosis due to shorter disease-free and overall survival both in node-positive and node-negative breast cancer[81 97 169 170] as well as lack of responsiveness to cytotoxic chemotherapies[92 171]. The data retrieved and incorporated into the model fit very well. The following rationale was applied in order to select and include the most appropriate data available in the published literature. The selection criteria for studies informing path- and transition probabilities were (1) randomised controlled clinical trials or published retrospective reviews of medical records, (2) studies with sufficient power, and (3) providing the required information (data points). Exclusion criteria were studies on phase II trials, conference abstracts, studies with very low sample size, studies of cancer therapies with monoclonal antibodies targeted against HER-2 other than trastuzumab and publications with insufficient information. For specific transition probabilities I have used the following data bases:

- **Disease free**: For information on disease progression out of the disease free health state I chose to incorporate the HERA trial in the model (as explained below).

- **Regional/ local recurrence**: Data sources were sparse for transition probabilities of patients with a regional or local recurrence. The studies by Harris et al.[172] and Shen et al.[173] were used. I was not aware of any other data source that would have allowed to extract the required amount of information.
- **Distant recurrence**: Using two studies providing progression rates according to HER-2 status and trastuzumab administration status, I was able to retrieve information on stable disease and mortality rates of metastatic breast cancer patients as required for the modelling[96 174]. There are other publications available[97 175-178], but the results were consistent with these studies. The publications by Slamon et al.[96] and Seidman et al.[174] were the only reports of randomised phase III trials of trastuzumab plus chemotherapy versus chemotherapy alone in metastatic breast cancer patients which enabled me to extract the information required for the modelling.

Modelling the disease free survival was based on the HERA trial, which assumed that HER-2 positive patients receiving trastuzumab treatment would have the same transition probabilities as patients receiving adjuvant trastuzumab in HERA[99]. In HERA, HER-2 positive patients were verified by IHC 3+ or FISH confirmation of IHC 2+ results. Accordingly, our analysis assumed that the same event risks were obtained with trastuzumab (i.e. the same transition probabilities have been applied to in the Markov model) in each of the combinations of FISH and IHC being tested. This implies that the HERA trial implicitly sets up a gold standard whereby the assumption of HER-2 positivity or negativity is made according to the results of the testing done in that trial, and the trial data applies to the patients identified. Hence, I did not take account the possibility that the event risk in HERA would have been different had a different system of HER-2 testing been used in that or other trials. When patients were identified by different test regimens and HER-2 positivity and negativity is not accurately predicted by this standard there could be a possibility that the measured benefits of trastuzumab would be different, namely less, than in the HERA study because of the different pattern of false positives and false negatives. Correction of these factors in each case would have required the determination of the “real” HER-2 status and the assumption of the benefit only in the true positive samples. The breast cancer model assumed that the same transition probabilities have been applied to each of the combination of IHC and FISH tests. It could be argued that the measured benefits of trastuzumab would be altered in the different test strategies, due to the fact of the variable pattern of false positive and false negative cases, as described above. This process would have needed complex modifications of the Markov model. By using hypothetical estimations, the effect on the base case result was only minor.

It should be noted, that the Breast Cancer International Research Group (BCIRG) clinical trial-data[110] was used as reference for FISH and IHC, but follow-up-data (i.e. survival times, risk of recurrence) after trastuzumab treatment was derived from the HERA trial[99]. Nevertheless, the assessment of sensitivity and specificity of test strategies does not depend on the effectiveness of trastuzumab treatment. Hence, no bias was introduced into the model by using the publication of Press et al[110] to extract data on sensitivity and specificity of IHC and FISH testing for HER-2 expression. I have chosen this basis for the following reasons: (1) there are only very few papers which discuss the sensitivity and specificity of these testing strategies; (2) the work by Press et al[110] is well accepted among

pathologists; (3) Press et al[110] provided the important information on false positive and false negative HER-2 testing results, which ultimately allowed me to model differences in clinical effectiveness (expressed in QALYs); and (4) the study was conducted with a considerable sample size (n=2600). Data on progression rates of HER-2 positive disease free patients treated with or without trastuzumab were derived from the HERA trial[99], due to the fact that the efficacy of trastuzumab in early breast cancer patients was presented in sufficient detail and allowed to inform the modelling of different health states in the health economic model (death, regional, local and distant recurrence). The BCIRG- studies[179] were not used as follow-up data as the published trial results did not provide me with the data requested for the model. Furthermore, some trials were not in accordance with the inclusion criteria mentioned above.

HER-2 positivity rate was assumed to range between 15% and 25%[81 88 90 180]. In the base-case, I assumed a HER-2 positive cohort of 20%. This rate has been varied within a range of 5% in diverse sensitivity analyses. However, there is recent evidence to suggest that the HER-2 expression level in the primary tumour differs from the invasive tumour tissue[181-185]. A discordant rate of about 5% to 10% is discussed. Accordingly, the data propose that the rate in early breast cancer is around 15% up to 20% while the rate in metastatic breast cancer is around 20% to 30%. This would imply a reassessment of the HER-2 status before treating advanced breast cancer patients. In addition, the sensitivity and specificity of the HER-2 testing regimens would probably need to be adapted according to the metastatic setting. Given the scarce data availability, I did not assess a HER-2 re-testing of patients in the metastatic cancer state.

Trastuzumab treatment duration of one year was assumed, which is the planned treatment schedule and also stated in the label[186]. Still, in the HERA trial 8.5% stopped treatment with trastuzumab before the completion of the one-year treatment period. Reasons were side effects, rejection or others[99]. Given that no information on mean or median treatment duration was available, I was not able to adapt the actual treatment time to the model. Moreover, there is evidence of anthracycline-based cardiac toxicity due to trastuzumab in combination with anthracycline chemotherapy[96 99 100]. Nevertheless, I did not take account possible side effects of trastuzumab or the standard chemotherapy, respectively. The main reason was the uncertain and inadequate data available for an accurate assessment in the Markov model.

The model evaded to assume any efficacy of trastuzumab administration to HER-2 negative patients. I have recognised that several open questions remain about the role of trastuzumab in treating breast cancer patients[187 188]. In the published literature, there are only a few studies addressing this topic. Seidman et al reported a randomised controlled trial showing no effect of trastuzumab in tumours lacking HER-2 overexpression or gene amplification[174]. However, study results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B-31[189] provided a counterbalance to the above mentioned study. Paik et al suggested that benefit from trastuzumab may not be limited to HER-2 positive patients, but their results were based on exploratory analyses and need to be verified in a phase III study[189]. Nevertheless, the concern of wrongly mislabelling patients as HER-2 negatives remains.

The present analysis adopted a Swiss health system perspective. This is an approach which is widely used in pharmacoeconomic evaluations. Hence, no indirect costs (e.g. loss of productivity) have been included. The loss of salary due to treatment-related absences from work is one of the greatest costs induced by the disease especially for cancer patients[190]. Most available data sources on indirect costs are based on conventional chemotherapeutic interventions. One was not able to estimate the extent of indirect costs for patients treated with trastuzumab. Therefore, the estimation of the indirect costs would be subject to great uncertainty. Furthermore, costs of the adjuvant chemotherapy were not incorporated. I expected that patients, regardless of trastuzumab administration, would have the same chemo-regimen resulting in any chemotherapeutic cost-difference in the treatment groups. The costs of aromatase inhibitors were included in the analysis as its administration varies according to the HER-2 status.

1.2. Test algorithm: points to consider

Recently, the American Society of Clinical Oncology and the College of American Pathologists (ASCO-CAP) recommend that HER-2 status ought to be determined for all invasive breast cancer, without giving priority to one test method[102]. They recommended either to use IHC assays for initial evaluation of HER-2 status followed by reflex FISH testing of some IHC categories or primary use of FISH in initial testing. Both assay methods have technical shortcomings resulting in different sensitivities and specificities of HER-2 testing. Our results support a previously published review favouring FISH over IHC testing for accuracy, reproducibility and precision reasons[79]. HER-2 gene amplification can be directly connected to the expression level of HER-2 protein[79]. Additionally, a positive FISH status points towards a much stronger responsiveness to trastuzumab. The use of FISH testing diminishes the number of patients eligible for trastuzumab therapy due to both superior sensitivity and specificity compared to IHC[79].

Evaluation of testing for HER-2 status should consider costs of treatment and testing as well as potential benefits of targeted therapy. FISH assays are significantly more expensive than the IHC assessment of HER-2. This is frequently used as an argument against primary FISH testing. Nonetheless, costs of diagnostic tests are minimal compared to the substantial costs of the therapy. This is especially important when considering that the cost of trastuzumab is approximately US$ 1’000 (equalling € 830) per treatment once a week for 52 weeks[191]. The present Markov model with an analysis of total costs and benefits clearly supports primary FISH testing as the most cost effective approach for patient management. However, the debate of whether IHC or FISH testing is more appropriate for the identification of HER-2 status cannot be solved by cost arguments only.

1.2.1. HER-2 testing in routine practice

In routine practice, many local laboratories only use IHC. Those patients with a positive IHC receive trastuzumab treatment. Numerous central laboratories use FISH for reflex testing of problematic IHC 2+ samples for quality assessment, as was the case in the HERA study[99]. In the USA, it is currently estimated that 80% of the HER-2 tests start initially with IHC and the rest is using FISH in the first instance[192]. However, both of these strategies were clearly dominated by the FISH testing regimen, as shown by our modelling results.

In Switzerland, many central laboratories have started to use FISH as the primary test. IHC is only added for equivocal cases. The strategy of verification FISH equivocal cases by IHC is difficult to assess, as no test sensitivity or specificity data for FISH equivocal samples (HER-2/CEP17 ratio signal between 1.8 and 2.2) were available from the literature. By using a tentative assumption of a theoretical sensitivity of 0.892[110 193], the clinical effectiveness yielded in 12.470 QALYs. Consequently, it can be assumed, that such a strategy would not achieve a further clinical benefit when compared to FISH alone. This aspect was comprehensively discussed in our publication[168].

1.2.2. False positive and false negative test results

Patients with false positive test results will be treated with the monoclonal antibody-based therapy although their benefit will be marginal. This may result in additional costs as well as risk of adverse events such as cardiac toxicity[96]. On the other hand, false negative results may have serious consequences for the cancer patient's prognosis. Approximately 3% to 4% of all early breast cancer patients are falsely negative[192]. Given that those patients do not receive anti-HER-2 targeted therapy, this implies an increased relapse rate or even death from failed adjuvant treatment. By sustaining high assay sensitivity, the incidence of false negative results may be kept small. In our cancer model, test sensitivity and specificity had a major impact on the base case result. It is not surprising, that treatment strategies with the highest rates of true positive results have ultimately yielded a favourable cost-effectiveness ratio (i.e. FISH testing).

It is assumed that 15% to 48% of equivocal IHC (2+) breast cancers indicate amplification of the HER-2 gene. Besides, IHC negative cases (0/1+) are FISH amplified in 2% to 8%. False positive IHC breast cancer samples which are lacking HER-2 amplification were found in about 5-22% cases[79 194]. This divergence may be mainly attributed to a loss in IHC sensitivity which is linked to tissue fixation[195]. HER-2 gene amplification identified by FISH is highly associated with patient survival, whereas such a relationship could only be found in strong immuno-stained samples (IHC 3+)[81 196]. In conclusion, FISH negative/ IHC positive patients have a similar prognosis as FISH negative/ IHC negative cases. Furthermore, FISH-positive/ IHC-negative breast cancer patients have a survival probability which is comparable to that of FISH-positive/ IHC-positive cases[195], as was assumed in our modelling analysis.

1.2.3. Novel test assays for HER-2 determination

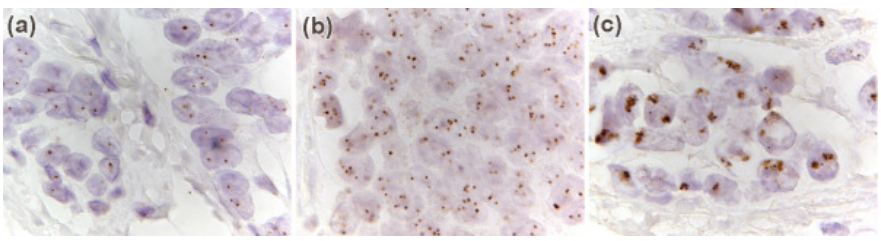


Figure 10. Chromogenic *in situ* hybridisation (CISH) on a breast carcinoma. a) normal HER-2 copy number; b) low level of HER-2 gene amplification (6 copies of HER-2 gene/cell); c) high level of HER-2 gene amplification. Resolution: 1000x. *Adapted from van de Vijver et al, Breast Cancer Res. 2007.*

There is a demand for new approaches for HER-2 status evaluation to amend the selection of patients treated with monoclonal antibodies. As a consequence, emerging new bright-field in situ hybridisation techniques for HER-2 assessment are currently being introduced[102]. Silver enhanced in situ hybridisation (SISH) compensates some shortcomings of FISH. This technique is characterised by a combined assessment of HER-2 and a chromomeric detection of chromosome 17,

its signal permanency and the usage of a bright-field microscopy to analyse the result[197 198]. The costs of SISH are, however, comparable with FISH. Similarly, chromogenic in situ hybridisation (CISH; SPOT-Light®, Invitrogen Corporation, Carlsbad, CA) identifies the level of HER-2 gene amplification by using a peroxidase-based chromogenic reaction, comparable with IHC (Figure 10)[199]. Accordingly, CISH results are determined by using a light microscope. Inter- and intra-laboratory concordance rates to establish testing techniques (IHC, FISH) are considered high, even in IHC equivocal cases[199 200]. Considering FISH as "gold standard", CISH proves sensitivity and specific rates of 85% (95% CI, 73%–95%) and 100% (95% CI, 100%–100%), respectively[201]. The HER-2 CISH kit was approved by the FDA in 2008[103]. Due to the fact that all clinical trials included in our model have not used CISH in assessing the HER-2 status of their patients, a CISH strategy was not included in the model. Furthermore, the CISH kit had some shortcomings and is not routinely used in all laboratories in Switzerland.

A recent technique which quantifies HER-2 expression and HER-2 homodimerisation in FFPE tissues is the HERmark Breast Cancer Assay (Monogram Biosciences, South San Francisco, CA)[202]. HERmark showed in a recent study high concordance (98%) with IHC positive and negative test results. Future studies are needed to assess the comparison of HERmark and FISH test assays from IHC negative, equivocal or positive cases[203].

2. Cost-effectiveness of metastatic breast cancer therapies

Herewith, the second publication (review article)[204] will be discussed.

While early breast cancer is fairly treatable, advanced cancer stages have a worse prognosis. If cancer cells metastasise to distant areas of the body, the patient may be treated, but not cured[205]. Currently, many ongoing studies measure the clinical effect of new therapeutic interventions in the late state disease of breast cancer patients. It is crucial to understand not only the clinical value but also the economic impact of new and existing treatments. In the UK, the annual costs of new metastatic breast cancer cases are estimated at £ 22 million (€ 23 million) for 2002. For the prevalent population, treatment costs of about £ 245 million (€ 308 million) are proposed[206].

Currently, many studies are dealing with cost and effectiveness of diverse novel treatment regimens for advanced breast cancer treatments. In the review article[204], I have reviewed pharmacoeconomic studies with regard to chemotherapy and targeted therapies for metastatic breast cancer patients. Endocrine therapy is generally given as first choice in the treatment of hormone receptor-positive patients[207]. Of note, in the review, I did not focus on endocrine treatment regimens. The review did not only focus on the incremental cost-effectiveness ratio achieved but moreover on the quality of the health economic evaluations. The key modelling parameters were also critically assessed. The guidelines described in section 1.7. (*Assessing quality aspects of health economic studies)* built the basis of the critical appraisal.

2.1. Treatment of metastatic breast cancer

The primary aim of treating metastatic breast cancer patients is mainly prolong survival, mitigate symptoms, and maintain quality of life[208]. The treatment of advanced breast cancer is not standardised. Patients can be treated with a single agent (monotherapy) or with a combination of agents, or single agents in sequence in order to diminish toxicity[209]. For the treatment of HER-2 positive cancer patients, trastuzumab is mainly used as first-line therapy in combination with or without chemotherapy[210].

2.2. Limitations of the review

There are some limitations associated with the present review. I included pharmacoeconomic studies from peer-review literature. The search of the studies was limited in terms of the database (MEDLINE). It can be assumed, that the database accessed maintains the majority of scientific full text articles. MEDLINE is considered the key source for reviews in terms of economic evaluations[211]. Hence, other databases such as CRED Evaluation Database and Embase were not searched. For the sake of not omitting important studies in this field, I consulted the reference list of the selected or related publications. This gave the review a broader basis. By manual searches and searches in databases other than MEDLINE some further studies might have been found, but the amount of additional information missed was assumed to be marginal[211].

The search criteria did exclude studies not written in English, as it is the general use in scientific review articles. Furthermore, I did not carry out a “gray literature search”, i.e. searching for studies which were not available in peer-reviewed journals. Consequently, information published by organisations or presented as abstracts at scientific meetings were omitted. This kind of information was not regarded as academically rigorous as the information which is available in peer-reviewed journals. I am aware that this may have lost some emerging new evidence of research. Nevertheless, with the information provided in an abstract, I would not have been able to extract information required for the sake of the quality assessments of the study. In the majority of meeting-abstracts, only scarce information on methodological issues is provided. This made it impossible to critically appraise the modelling process and the parameter values included in the analysis.

The studies included were of diverse methodological rigor. The results of the cost-effectiveness studies could hardly be compared with each other, as they all originated from different countries, using different modelling methodologies as well as input parameters. The ICER reported for the different agents showed a broad spectrum. For the sake of reimbursement decisions, pharmacoeconomic results are usually compared to reference thresholds or other cost-effectiveness analyses. The reference value may be based e.g. on societal willingness-to-pay levels (see also Introduction, 1.8.1.)[46].

The health economic studies of cytotoxic therapies generally showed favourable cost-effectiveness ratios (i.e. rates below the threshold values). Considering the review results, no preference for the one or the other agent could be determined. Targeted therapies, in particular trastuzumab, showed favourable and non-favourable results. Given that most information on the health economic impact of

targeted non-chemotherapeutics for metastatic breast cancer treatment was focused on trastuzumab, it was inevitable to pay special attention to this agent. From a European third-party perspective, Norum et al[212] appraised the first-line therapy of trastuzumab combined with chemotherapy as not cost-effective (compared to chemotherapy alone in HER-2 positive patients). In contrast, NICE evaluated trastuzumab treatment both as mono-therapy and in combination with paclitaxel as cost-effective for HER-2 positive metastatic breast cancer patients[213 214]. This implies that different parameters (costs and effects), different modelling approaches and different perspectives considerably influence health economic data.

The majority of pharmacoeconomic evaluations used models based on indirect data inputs from the published literature. The associated limitations with modelling have been discussed extensively (see Introduction, 1.6.). Nevertheless, the realisation of pharmacoeconomic studies requires the assessment of best practices for the sake of quality of evidence[215]. In the review article, we discussed the underlying data that were used in the models to assess whether the assumptions are credible, relevant (incremental) costs and effects were included, and how studies extrapolated e.g. progression free survival to life-years gained.

Most studies have not included indirect costs because of their chosen perspective (e.g. third party perspective). Notably, for metastatic breast cancer patients the work capacity is limited. Often, they are forced to go into early retirement[216]. Moreover, the economic and occupational burden of care givers is substantial[217]. The perceived burden has been shown to be negatively associated with the functional status of the breast cancer patients.

I only included studies published since the year 2000 in order to have a comparable study population in both the conventional and targeted treatment setting. Nevertheless, some of the studies were conducted before generic tamoxifen or paclitaxel were available. This implies that current drug costs may be lower than reported in these studies. The conclusion on whether an agent is cost-effective may vary according to price-cuts in some countries or new dosing schemes.

2.3. Concluding remarks

The actual cancer treatment patterns have an enormous influence on the costs and effects of cancer therapies in the metastatic setting. In order to efficiently utilise resources in the management of advanced breast cancer, it is crucial to better understand the health economic implication of those interventions. Pharmacoeconomic evaluations are one key element in providing important information to physicians, patients, insurers, pharmaceutical and other industries, healthcare policy planners, and others[218]. The present review suggests that gaps in the literature especially with regard to high quality economic models are considerable. There is an implicit need of studies, evaluating the pharmacoeconomics of current cancer drugs and how they might change the current clinical practice.

3. Health economic implication of testing for KRAS and BRAF mutation

The introduction of molecular tests into the clinical management of metastatic colorectal cancer patients which are treated with EGFR-targeted drugs, is a great goal achieved by researchers. These predictive tests are very important for the identification of patients who might benefit from these agents, but they are also rather expensive. In order to validate whether molecular tests on the management of metastatic colorectal cancer are economically favourable, I assessed in my second PhD study programme the costs and effects of different testing strategies for KRAS and/or BRAF prior to cetuximab treatment of metastatic colorectal cancer patients (third paper, submitted manuscript). Costs were considered from the perspective of the Swiss health system. By using a life-long Markov simulation model, the sequential approach with BRAF testing of all KRAS wild-type patients was identified as the test strategy with the most favourable incremental cost-effectiveness ratio of the approaches investigated (ICER: € 67'779/QALY compared to no cetuximab). The present work is the first study assessing the health economic implications of testing for KRAS and/or BRAF gene mutations in metastatic colorectal cancer. The strengths of the study include the evaluation of a clinically relevant policy topic and high quality data sources.

3.1. Limitations of the analysis

In the manuscript of the second part of my PhD programme the main limitations have been discussed. Some of these and some further points are elucidated here.

First of all, cetuximab is not the only EGFR-targeted therapy approved for the treatment of advanced colorectal cancer patients, although it represents the most common choice. Hence, I could have run the entire model with other monoclonal antibodies targeted against EGFR, as e.g. panitumumab (Vectibix®, Amgen, Inc). Randomised controlled phase III studies indicated similar effects with this drug, which allowed to assume that using another targeted therapy would achieve comparable outcomes. My first interest was to provide information on the impact of predictive test strategies before using antibody therapy. I was not focusing on whether one drug was superior to an alternative treatment.

Some further limitations are related to the availability of the included data. I started by clearly defining the patient population of interest and tried to determine the most suitable model inputs available from the published literature. Due to the fact that clinical evidence from pivotal studies is limited, I mainly used clinical efficacy from trials conducted outside of Switzerland[121 129 219 220]. The model assumed that patients with BRAF mutation receiving best supportive care would have the same transition probabilities as patients receiving best supportive care with a KRAS mutation[129]. This postulation is based on similar non-response of KRAS and/or BRAF mutated tumours to EGFR-based agents[141]. To the best of my knowledge, there is no real world data available on the response rates of untreated patients harbouring BRAF mutation, backing this assumption.

Data on utility as well as quality of life were restricted. Information on utility came from the CO.17 trial conducted by the National Cancer Institute of Canada Clinical Trials Group[219]. Compared to Switzerland, there might be some differences in the clinical treatment schedule or perception of quality of life. However, while being aware of this limitation, I have included the foreign data as the best available source of clinical evidence. One was able to distinguish utilities according to the treatment received but not on the basis of mutation status. Given the fact that both BRAF and KRAS mutation is linked with a comparable lack of response to anti-EGFR therapies[141], the quality of life in non-responders was assumed to be similar to patients treated with best supportive care. In the base case analysis the differences in the QALY results were primarily driven by the variation in survival times determined by the mutation status and anti-cancer therapy. This instance has been fully integrated into the analysis.

Information on the prognostic compared to predictive value of BRAF was derived from various studies. Until now, there is broad discussion on whether BRAF is a firm molecular marker. It is not entirely clear to what degree BRAF is prognostic for outcome with no treatment or predictive for the result of cetuximab treatment. Clinical research showed strong evidence favouring BRAF testing[141 220]. Furthermore, in Switzerland, BRAF testing has only entered the laboratories of pathologies recently. To bear with the uncertainties regarding the genomic association data for BRAF, numerous sensitivity analyses have been carried out to assess the robustness of the study results.

The Markov model used a time frame, which was life-long for the base case analysis. Yet, I based the assumptions of the overall survival rate and risks for progression on clinical trials which had a shorter time frame[129 219 220]. It is argued that the life-long scenario is associated with more uncertainty and in general a better cost-effectiveness ratio[221]. Nevertheless, the life-long approach is in line with good health economic practice for the evaluation of interventions with life-long consequences or a survival influence[222]. In a sub-analysis I determined the cost and effects of using a time frame of 18 months, which is also in agreement with the trial duration of CO.17[219]. Testing for KRAS and BRAF remained the preferred strategy with an ICER of € 108'425/QALY compared to the reference of no cetuximab. The next best strategy was KRAS testing yielding a much higher cost-effectiveness ratio (€ 580'263/QALY compared to KRAS/BRAF testing). These results agree in principle with the results found by Mittmann and colleagues who conducted an economic within-trial analysis of cetuximab therapy compared to best supportive care in KRAS wild-type patients (€ 144'360 per QALY gained)[219]. Their analysis was restricted to the observation period of the CO.17 trial (18-19 months)[121 219]. They calculated an ICER which is much higher than my life-long base-case results, but similar to my short-term analysis. The favourable ICER in my base-case analysis can be attributed to the fact of a higher accumulation of QALYs gained due to the incorporation of the full survival experience of all patients inclusive of longer-term survivors. In addition to this, the Canadian study did not include the costs of the mutation testing, as all patients in their cohort were tested. However, extrapolating their estimates to the general population would require the inclusion of the test costs[223]. This approach is of particular importance when different test assays, different biomarkers and different test strategies are taken into account, which was the case in my analysis.

Data on clinical resource use was mainly based on the information derived from clinical trials, but divergence from routine practice patterns may occur. In a sub-analysis, I varied the usage of diagnostic procedures in the best supportive care group but could not find an influence on the base case results. Moreover, resource usage was discussed extensively with clinical practitioners for its appropriateness. For an accurate assessment of the costs to the Swiss Health Care System, costing data (including hospitalisation) derived from the official Swiss tariff book (Tarmed), official Swiss pharmacy prices and Swiss hospital statistics were used[224 225 226 227].

There are studies which have provided information on adverse events of cetuximab treatment[138 219]. It can be assumed, that avoiding such effects in non-responders is another important benefit of predictive testing. As in the breast cancer model[168], I realised that I could not fully include this aspect. I have, however, indirectly taken into account some costs of adverse effects by including times of hospitalisation which may have been, at least in part, related to treatment toxicity.

Given the third-party perspective of the analysis, indirect costs were not included. Nevertheless, it should be noted that indirect costs as e.g. productivity loss may have considerable influence on the economic burden of the disease, but they are hard to measure. Recent research identified that most of the working non-metastatic colorectal cancer patients return to work. About 17% quit workforce which can be mainly attributed to worse prognosis or low socioeconomic status[228]. Hence, it is unsure, to what extent, patients on cetuximab last-line therapy are capable to hold an occupation or are able to continue to work. Moreover, patients receiving cetuximab have to visit the hospital on a weekly basis which implies increased productivity costs. Noteworthy, the economic burden of informal care givers of colorectal cancer patients can be assumed as considerable[229]. In a cross-sectional survey, Van Houtven and colleagues measured the economic implications in terms of opportunity costs of caregiver time, the value of lost work hours and out-of-pocket expenditures. Depending on the patient's disease phase, the economic burden for caregiver ranged between US$ 7'028 (€ 5'493) and US$ 14'234 (€ 11'125).

The strength of the present analysis is the distinction of different testing strategies and their impact on the cost and effects in the EGFR-targeted colorectal cancer treatment. There are no studies available which examined different testing strategies including BRAF mutation analysis.

3.2. Emerging clinical evidence

3.2.1. Novel potential molecular markers

On one hand the activation of downstream EGFR pathways is mediated by KRAS and BRAF and by PIK3 on the other hand. However, absent KRAS and/or BRAF mutations do not warrant response to monoclonal antibody treatments. The sensitivity to these drugs demands for wild-type KRAS/BRAF phenotype, but there are still patients, who do not respond to cancer therapy with cetuximab or panitumumab[127]. This indicates that other molecular targets might be involved in the downstream pathway of EGFR. Due to the complexity of the signalling pattern, it is likely that future predictive test assays will include several molecular biomarkers before antibody treatment. There are further candidates discussed by the scientific community for refining the responding patient population

including the expression level of EGFR copy number and expression levels of EGFR ligands, loss of phosphatase and tensin homolog (PTEN) or markers of the angiogenesis and cell cycle regulation as the vascular endothelial growth factor (VEGF), Interleukin-8 (IL-8), cyclooxygenase-2 (COX-2), cyclin D or nuclear factor kappa B (NFκB)[230]. However, the validity of those makers has not yet been established and further research is needed. Some of these candidates will be discussed hereafter.

Predictive testing algorithm revised

Clearly, mutated KRAS or BRAF are not the only factors that determine response to anti-EGFR cancer therapy. A considerable proportion of patients can be found which neither have a mutation on KRAS nor in BRAF, but still do not respond to EFGR monoclonal antibodies[231]. This implies that new predictive makers in the colorectal cancer setting are of great need. The determination of BRAF, PIK3, PTEN or EGFR gene copy status may offer detailed information whether patients may respond to EFGR-targeted therapies (Figure 11) [231-233]. The appraisal of costs and effectiveness of new test assays is pending.

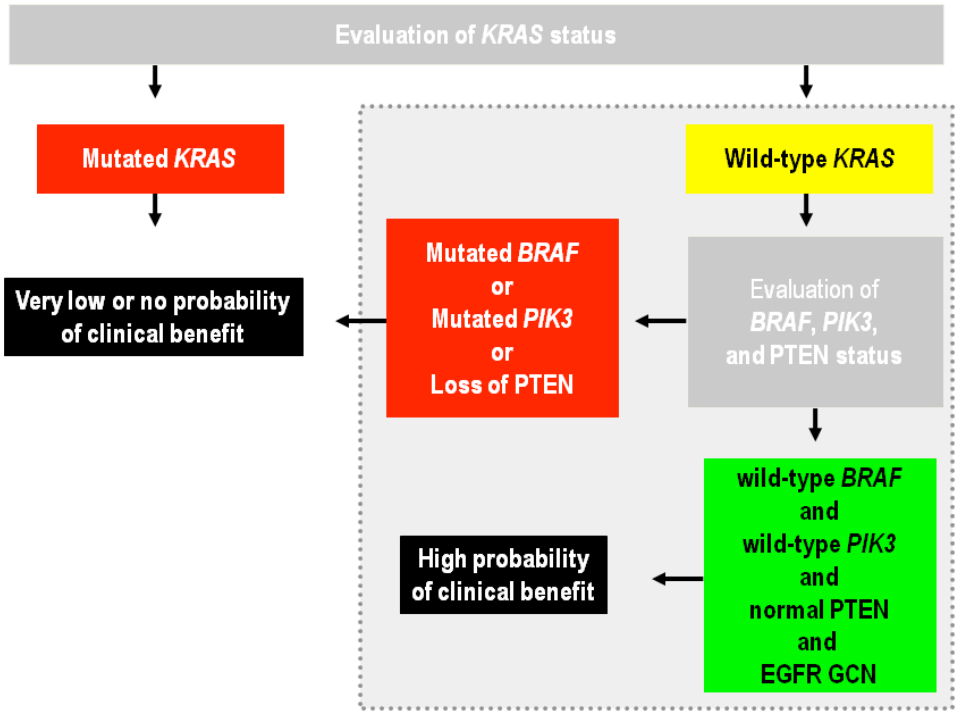


Figure 11. Prospective algorithm of colorectal cancer patients. GCN: gene copy number. *Adapted from Sartore-Bianchi et al, Cancer Res, 2009.*

EGFR

The relationship between EGFR expression level and response to anti-EGFR monoclonal antibody therapy has been shown to be minor[122]. Colorectal cancer patients not expressing EGFR, as detected by IHC, have a potential to benefit from cetuximab-based therapy[234]. The detection of protein expression by IHC has comparable shortcomings as already discussed in the sections above (e.g. fixation, storage of unstained tissue sections or methodology of IHC evaluation). Moreover, the expression level of EGFR is assumed to differ between the primary and the advanced tumour[235]. Given this, the predictive value of EGFR determination by IHC techniques seems to be uncertain[233].

There is evidence, that patients with an increase in EGFR gene copy number, as determined by FISH or CISH, reveal a higher response to EGFR targeted therapies. Compared to patients with normal gene amplification, progression free survival was enhanced in those patients exhibiting a higher number of EGFR gene copies[236 237]. Hence, the detection of EGFR gene status may represent a predictive factor for the response of monoclonal antibody therapies targeted against EGFR (Figure 11)[233]. Nevertheless, the methodological techniques have to be further standardised for achieving elevated reproducibility and sensitivity[238].

PTEN and PI3K

The phosphatase PTEN de-phosphorylates phosphoinositide (PI3) and thereby controls the activity of its kinase (PI3K) (Figure 7). The loss of PTEN results in constitutive signalling of PI3K and apoptotic resistance. It has been shown that deregulated PI3K or PTEN gene as well as loss of PTEN protein expression conferred diminished response to cetuximab therapy in colorectal cancer patients[232 236 239]. By assessing the PTEN expression status by IHC in primary colorectal cancer patients and their metastatic tumours, Loupakis demonstrated considerable differences in the number and staining intensity of PTEN-positive cells[240]. In metastatic tumours, PTEN expression status was found to be highly correlated with tumour response and progression free survival in irinotecan and cetuximab treated patients. The predictive role of PTEN in KRAS mutated patients is, however, not yet validated and additional results from larger trials are needed[24 241]. Moreover, the evaluation of PTEN requires standardisation and its introduction in the clinical setting is not yet established (Figure 11)[233].

3.2.2. Randomised studies for first-line treatment

Several randomised studies assessed the effect of cetuximab as first-line treatment when administered in combination with standard chemotherapy[159 242 243]. The CRYSTAL (cetuximab combined with irinotecan in first-line therapy for metastatic colorectal cancer) study determined superiority of the cetuximab-combination treatment in terms of risk of progression of metastatic colorectal cancer[159]. The benefit of cetuximab was restricted to KRAS wild-type patients. BRAF mutation was not identified as predictive marker for cetuximab response in first-line treatment of advanced colorectal cancer. The OPUS trial involved chemonaive metastatic colorectal cancer patients treated with cetuximab and chemotherapy (oxaliplatin) or chemotherapy alone[242]. The subgroup of KRAS wild-type patients revealed a significant survival benefit when the combination therapy was administered.

3.2.3. Health economic impact of colorectal cancer management

Drug costs for e.g. colorectal cancer may range from less than US$ 100 (€ 79) to over US$ 50’000 (€ 39’081) for a six-month systemic therapy with fluorouracil/ leucovorin administered daily for 5 days each month and weekly cetuximab monotherapy, respectively[64]. Recently, Wong and colleagues assessed the cost implications of treating advanced colorectal cancer patients with sequential regimens of cytotoxic and targeted therapies[67]. By using a Markov model incorporating only drug costs, new chemotherapeutic agents resulted in an ICER of US$ 100’000 (€ 79’000) per discounted life year (DLY). By adding antibody-based treatment regimens, the ICER increased to more than US$ 170’000/DLY. Hence, the authors concluded that even the most effective treatment regimens lead to a

high cost-effectiveness ratio. These results underline the importance of health economic evaluation in the field of cancer patient management. Clinically valuable predictive tests for the prediction of drug response are one keystone in the realisation a cost-effective implementation of new and effective cancer therapies. Results of pharmacoeconomic evaluations should help to inform future guidelines of using such tests.

Part VI – Conclusion

Limited data is available on the variations in predictive testing practices in cancer care. Understanding the application of predictive assays is crucial in targeted cancer therapies. The present study results may help to inform the recent debate on advantages and disadvantages of alternative testing strategies for selecting patients for breast and colorectal cancer treatment schedules.

For the Swiss setting, primary FISH testing with subsequent adjuvant trastuzumab treatment of HER-2 positive breast cancer patients was determined as the most cost-effective and hence preferable approach. For the metastatic colorectal cancer patients, it is economically favourable to test both for KRAS and BRAF mutations before treating patients with cetuximab. The analytic framework regarding HER-2, KRAS and BRAF testing illustrates the challenges and opportunities in building a basis of evidence to sustain successful decision making about novel and emerging test assays in cancer management.

We have only begun to investigate the health economic role of predictive testing. It would be of interest to elucidate the impact of testing in many other settings. Currently there are numerous novel predictive assays which are introduced into clinical pathology. Future steps may include the evaluation of costs and effects of testing for EGFR mutations in non-small-cell lung cancer, or for a 21-gene signature to predict the likelihood of chemotherapy benefit as well as recurrence in early stage, node-negative, oestrogen receptor-positive breast cancer patients.

The strength of these projects is that the analytic framework showed the importance of testing for the targets of new molecular targeted agents. By selecting patients who are more likely to respond based on such a predictive test result, the most efficient approach to using an expensive therapy in a population can be realised.

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List of abbreviations

AKT, Protein kinase B

ASCO, American Society of Clinical Oncology

ASCO-CAP, American Society of Clinical Oncology and the College of American Pathologists

BRAF, Serine/ threonine-protein kinase B-Raf

DLY, Discounted life year

DNA, Deoxyribonucleic acid

CEP17, Chromosome 17

COX-2, Cyclooxygenase-2

EGFR, Epidermal growth factor receptor (ErbB1/ HER-1)

ErbB2, HER-2/neu

ErbB3, HER-3

ErbB4, HER-4

FDA, Food and Drug Administration (USA)

FFPE, Formalin-fixed, paraffin-embedded

FISH, Fluorescence in situ hybridisation

GCN, Gene copy number

GDP, Gross domestic product

HER, Human epidermal growth factor receptor

ICER, Incremental cost-effectiveness ratio

IHC, Immunohistochemistry

IL-8, Interleukin-8

JAK, Janus kinase

KRAS, Kirsten rat sarcoma viral oncogene homolog (V-Ki-ras2)

LYG, Life year gained

MAb, Monoclonal antibody

MAPK, Mitogen-activated protein-kinase

MSI, Microsatellite instability

NFκB, Nuclear factor kappa B

NICE, National Institute for Health and Clinical Excellence

PCR, Polymerase chain reaction

PI3K, Phosphatidylinositol triphosphate kinase

PTEN, Phosphatase and tensin homolog

QALY, Quality-adjusted life-year

RAF, Proto-oncogene serine/ threonine-protein kinase

RT-PCR, Reverse-transcriptase polymerase chain reaction

STAT, Signal Transducers and Activators of Transcription

UK, United Kingdom

USA, United States of America

VEGF, Vascular endothelial growth factor

WHO, World Health Organization

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11.2007 - present	**Assistant lecturer, Faculty of Medicine, University of Zurich, Switzerland**
	Mantelstudium Medizin “Einführung in die Arzneimittelentwicklung”
4.2007 - present	**Assistant lecturer, Faculty of Science, University of Zurich, Switzerland**
	BIO 410 “Research methodology for studies on human health and disease”;
	BIO 429 “Developing New Medicines – An Introduction”

PUBLICATION LIST

Peer-review articles

Blank PR, Schwenkglenks M, Moch H, Szucs TD (2010): Human epidermal growth factor receptor 2 expression in early breast cancer patients: a Swiss cost-effectiveness analysis of different predictive assay strategies. Breast Cancer Res Treat 25;10(1):4.

Blank PR, Dedes KJ, Szucs TD (2010): Cost Effectiveness of Cytotoxic and Targeted Therapy for Metastatic Breast Cancer: A Critical and Systematic Review. Pharmacoeconomics 28(8):629-47.

Widmer LL, **Blank PR**, Van Herck K, Hatz C, Schlagenhauf P. Cost-effectiveness analysis of malaria chemoprophylaxis for travellers to West-Africa. BMC Infect Dis 2010;10(1):279.

Blank PR, Blank AA, Szucs TD (2010): Cost-effectiveness of oral alitretinoin in patients with severe chronic hand eczema: a long-term analysis from a Swiss perspective. BMC Dermatol 10:4.

Michel JP, Gusmano M, **Blank PR**, Philp I (2010): Vaccination and healthy ageing: How to make life-course vaccination a successful public health strategy. European Geriatric Medicine, article in press.

Blank PR and Szucs TD (2009): "Increasing influenza vaccination coverage in recommended population groups in Europe." Expert Rev Vaccines 8(4): 425-33.

Endrich MM., **Blank PR**, Szucs TD (2009): "Influenza vaccination uptake and socioeconomic determinants in eleven European countries." Vaccine 27:4018-24.

Blank PR, Schwenkglenks M, Szucs TD (2009): "Vaccination coverage rates in eleven European countries during two consecutive influenza seasons." Journal of Infection, 58:446-58.

Blank PR, Schwenkglenks M, Szucs TD (2009): "Disparities in vaccination coverage rates by target group in five European countries during the influenza season 2007/08." Infection 37(5):390-400.

Blank PR, Schwenkglenks M, Szucs TD (2008): "Influenza vaccination coverage rates in five European countries during season 2006/07 and trends over six consecutive seasons." BMC Public Health **8**: 272.

Nicoll A, Ciancio B, **Blank PR** et al. (2008): "The scientific basis for offering seasonal influenza immunisation to risk groups in Europe." Euro Surveill 13(43).

Blank PR, Freiburghaus AU, Ruf BR, Schwenkglenks M, Szucs TD: Trends in influenza vaccination coverage rates in Germany over six seasons from 2001/02 to 2006/07 (2008): Med Klin (Munich) 103:761-8.

Blank PR, Freiburghaus AU, Schwenkglenks M, Szucs TD: Influenza vaccination coverage rates in the UK over six seasons from 2001/02 to 2006/07 (2008). Eurosurveillance 23;13(43).

Blank PR, Schwenkglenks M, Szucs TD, Kunze U (2008): Influenza vaccination coverage rates in Austria in 2006/2007. Wiener Medizinischen Wochenschrift 158(19-20):583-8.

Holm MV, **Blank PR,** Szucs TD: Influenza Vaccination Coverage Rates in Europe - Covering Five Consecutive Seasons (2001-2006) in Five Countries (2008): Influenza and Other Respiratory Viruses 1(5-6):215-221.

Holm MV, **Blank PR**, Szucs TD: Developments in influenza vaccination coverage in England, Scotland and Wales covering five consecutive seasons from 2001 to 2006 (2007): Vaccine 25:7931-8.

Holm MV, **Blank PR**, Szucs TD: Trends in influenza vaccination coverage rates in Germany over five seasons from 2001 to 2006 (2007): BMC Infect Dis 7:144.

Book chapters

Thiersch M, Raffelsberger W, Frigg E, Samardzija M., **Blank PR**, Poch O and Grimm C (2008): The hypoxic transcriptome of the retina: identification of factors with potential neuroprotective activity. Adv Exp Med Biol 613:75-85, 2008

Bulletin articles

Blank PR (2008): "Report on DG Sanco's Vaccination Strategy Workshop 13-14 February 2008." The Influenza Bulletin, The European Scientific Working group in Influenza (ESWI) 24.

Blank PR, Szucs TD. (2008): "Seasonal influenza vaccination in Europe: 2006/07 coverage rate in 11 European countries." The Influenza Bulletin, The European Scientific Working group in Influenza (ESWI) 23.

ATTENDED COURSES AND LECTURES DURING MY PHD

FS 2010	**Postgraduate course in effective scientific presentations in the Sciences or Medicine**
	Transferable Skills, University Zurich, Switzerland (certified)
1.2010 - present	**Frontiers in Drug Development - ECPM Education Seminars** (certified)
10.2008	**Tree Age Pro Standard Healthcare Training: two-day modelling course, Basel, Switzerland**
10.2007 - present	**Colloquium Institute of Surgical Pathology, University Hospital Zurich, Switzerland**
2.2007 - present	**Colloquium Institute of Social and Preventive Medicine, University of Zurich, Switzerland**

INVITED ORAL PRESENTATIONS

12.2010	**Influenza Vaccination and Communication Meeting, European Center for Disease Prevention and Control (ECDC); Stockholm, Sweden**
9.2010	**Options for the Control of Influenza VII (Options VII)), Hong Kong, China**
	"Worldwide community attitudes towards the 2009 pandemic vaccination and impact on the acceptance of seasonal flu vaccination"
5.2010	**94. Jahrestagung Deutsche Gesellschaft für Pathologie e. V., Berlin, Germany**
	"Human Epidermal Growth Factor Receptor 2 (HER-2) Expression in Breast Cancer Patients: A Swiss Cost-Effectiveness Analysis of Different Predictive Assay Strategies"
11.2009	**European Public Health Association (EUPHA), Lodz, Poland**
	"Determinants of implementation of 50+ vaccination in Europe: experience with seasonal influenza vaccination"
9.2009	**Colloquium Institute of Surgical Pathology, University Hospital Zurich, Switzerland**
	"Human Epidermal Growth Factor Receptor 2 Expression in Breast Cancer Patients"
5. 2009	**2nd Influenza Forum - The Influenza Paradox: strategies for improving uptake in healthcare workers (HCW), Brussels, Belgium**

"Policy issues related to HCW"

4.2009 **3rd International Conference on the Influenza Vaccines for the World, Cannes, France**

"Societal perspectives and challenges of influenza vaccination"

11.2008 **Colloquium Institute of Social and Preventive Medicine, University of Zurich, Switzerland**

"Health Economics in Oncology in Switzerland"

10.2008 **European Respiratory Society (ERS) Congress, Berlin**

"Societal perspective and challenges of influenza and pneumococcal vaccination in patients at risk of respiratory complications"

2.2008 **Vaccination strategy workshop, Public Health Executive Agency (PHEA), European Commission of Public Health, Luxemburg**

"Seasonal Influenza Vaccination in 11 European Countries 2006/7 survey – Drivers, barriers and cost benefit of the flu vaccine"

5. 2007 **European Influenza Surveillance Scheme (EISS) meeting, Malaga, Spain**

"Flu Vaccination in Europe - Influenza Vaccination Coverage Rates 2006/ 2007 in four Countries: Germany, Italy, Spain, United Kingdom"

POSTER PRESENTATIONS

9. 2010 **Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Boston USA**

"Cost-effectiveness of 13-valent pneumococcal conjugate vaccine in Switzerland"

8.2010 **European Society of Cardiology, Stockholm, Sweden**

"Cost-effectiveness of ferric carboxymaltose in patients with chronic heart failure: an analysis from the FAIR-HF trial"

6.2010 **American Society of Clinical Oncology (ASCO) Annual Meeting 2010, Chicago USA**

„Cost-Effectiveness of K-Ras Testing in the Colorectal Cancer Setting"

6.2010 **XLVII ERA-EDTA and II DGfN Congress, Munich, Germany**

"Economic Benefits of Anaemia Management Using ESAs and Intravenous Iron Supplementation in Non-Dialysis-Dependent-CKD Patients"

12.2009 **Annual Meeting of the American Society of Hematology (ASH), New Orleand, USA**

"Cost-effectiveness of ferric carboxymaltose supplementation in patients with ESA treated chemotherapy-induced anemia"

10.2009 **42nd Annual Meeting of the American Society of Nephrology (ASN), Renal Week 2009, San Diego, USA**

"Health Economic Impact of Intravenous Iron Supplementation in Anemia Treatment with Erythropoiesis−Stimulating Agents in CKD Patients"

6.2009 **American Society of Clinical Oncology (ASCO) Annual Meeting 2009, Orlando USA**

"Cost-Effectiveness of Predictive Markers in the Breast Cancer Setting – An Analysis from a Swiss Perspective"

9.2008 **3rd ESWI (European Scientific Working group on Influenza) Influenza Conference, Vilamoura, Portugal**

"Influenza vaccination coverage rates in four European countries during winter of 2007/08"